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THE THYREOTROPHIC HORMONE AND ITS RELATION TO CLINICAL SYNDROMES.

By C. G. LAMBIE.

(From the Department of Medicine, University of Sydney.)

RECENT research has greatly enlarged our knowledge of the relationship between pituitary secretion and the functions of the thyreoid gland, and it seems desirable to review present opinions, coordinating the conclusions of experimental workers with the observations of clinicians. I propose to deal with the subject in two parts. In the first I shall discuss the isolation, physico-chemical properties and physiological action of the thyreotrophic hormone, and in the second the relation of the hormone to clinical syndromes.

PART I.

IDENTIFICATION, PURIFICATION, ASSAY, PHYSICO-CHEMICAL PROPERTIES AND PHYSIOLOGICAL ACTION OF THE THYREOTROPHIC HORMONE.

IDENTIFICATION.

If we accept some of the older anatomical evidence, based chiefly upon *post mortem* examinations, our knowledge of the control of thyreoid function by the pituitary gland may be said to go back some fifty years. In 1899 Ponfick published an important paper entitled *"Myxödem und Hypophyse"*, describing a case of myxœdema in which the changes in the pituitary were much more advanced than those in the thyreoid: the glandular portion of the pituitary had been largely reduced to fibrous tissue, it was cystic and partially calcified; the thyreoid, on the other hand, showed only a moderate degree of atrophy. Two years previous to the

appearance of Ponfick's paper, Coulon[53] had described a series of five cases diagnosed as cretinism, in which atrophic changes were alleged to have been present in the pituitary; but the patients were adults, no details were given regarding the clinical findings beyond the statement that the patients exhibited the "cretinic habitus", and the changes in the pituitary were indefinite, some of the glands being increased, others diminished in size with a diminution in chromophile cells. Later, Maresch[192] described a case somewhat similar to that of Ponfick.

That the pituitary exerts an important influence upon the thyreoid has long been considered probable in view of the secondary effects of pituitary lesions, whether these be associated with syndromes of deficiency or of excess. Thus in patients suffering from Simmonds's pituitary cachexia,[272] in which extensive changes are present in the pituitary, the thyreoid is found to be atrophied.[96] Again, some pituitary tumours may be associated with clinical appearances suggestive of hypothyreoidism; others, such as the eosinophile adenoma, may be accompanied not only by acromegaly, but by signs of hyperthyreoidism and even exophthalmic goitre.[57]-[135][109][305][75][7][117]

The conclusions to be drawn from these older anatomical and clinical observations may be regarded as conjectural rather than affording actual proof of pituitary control of thyreoid function and it is necessary to ascertain how far they agree with the results of experimental investigation. From what follows it will become evident that experiment not only confirms these tentative conclusions, but has revealed the mechanism by means of which the pituitary exerts its control over the thyreoid.

Experimental procedure has followed the usual lines adopted in dealing with physiological problems of this character, namely, a study of the effects of (*a*) destruction or ablation of the pituitary, (*b*) substitution therapy in animals deprived of the pituitary, and (*c*) administration to intact animals of excess of the active principle concerned.

The history of investigations upon the identification and physiological action of the thyreotrophic hormone may be divided into two periods. In the earlier experiments only grafts or crude extracts of pituitary substance, containing a mixture of hormones and other impurities, were available; while in the more recent work purified extracts, more or less free from contamination with other hormones, have been employed.

Older Experimental Investigations.

Ablation.

Metamorphosis of Amphibia.—Much work of fundamental importance regarding the pituitary-thyreoid relationships has been done upon amphibia. It has long been known that removal of the thyreoid gland prevents the metamorphosis of neotenous amphibia; but Adler,[4] Allen[5] and Smith[278] have found that removal of the pituitary gland from tadpoles also causes a failure to metamorphose.

Morphological Changes in the Thyreoid.—Hypophysectomy in tadpoles likewise induces the resting phase of thyreoid activity, as shown by increase in colloid followed by atrophy,[4][5][278] suggesting that the failure to metamorphose is due to secondary thyreoid involution and functional insufficiency. The changes in the thyreoid of tadpoles are similar to those previously reported by Cushing[56] and by Aschner[25] following hypophysectomy in the dog. Cushing states that in this animal removal of the pituitary results in transient hyperplasia followed by involution changes—a flattening of epithelium and increase of colloid. Functional involution and atrophy have also been observed after hypophysectomy in the rat.[80][276][230]

Metabolism.—Some of the earliest experiments upon the physiological results of extirpation of the pituitary were made with reference to the effect of this operation upon the metabolism of the dog. Benedict and Homans,[26] Cushing[56] and Aschner[25] found that removal of the gland was followed by a lowering of metabolism—an observation which has been confirmed by Koster and Giesink.[143] Similar findings were also obtained by Foster and Smith[80] in the rat.

Substitution.

It has been demonstrated both in tadpoles[278] and in the rat[80][276] that the effects of ablation of the pituitary upon metamorphosis, involution of the thyreoid and metabolism can be prevented by homologous grafting of pituitary gland or by parenteral injection of pituitary substance or crude extracts of bovine pituitary anterior lobe.

Excess.

Metamorphosis of Amphibia.—Transplantation of the hypophysis of adult frogs[6] or the injection of crude extracts of anterior lobe substance[279] into tadpoles accelerates metamorphosis. These procedures also initiate metamorphosis in axolotls.[118][280] Hogben[118] reported that pituitary extracts caused metamorphosis even in thyreoidectomized axolotls, a result confirmed by Spaul.[20][281] Other experimenters,[298][259][260] on the other hand, have failed to obtain metamorphosis or a rise in metabolism after treatment with thyreotrophic extracts in thyreoidless axolotls, suggesting that the action of pituitary extract is an indirect one through the thyreoid.

Morphological Changes in the Thyreoid.—Injection of crude extracts or heteroplastic implants of pituitary substance into intact neotenous amphibia also caused thyreoid hyperplasia with disappearance of colloid.[297-301][130][94][95]

Metabolism.—Schwartzbach and Uhlenhuth[259][260] also found that injection of crude pituitary extracts was followed by a rise of metabolism in axolotls.

Recent Experimental Work.

The years 1929-1930 mark the transition to the more recent phase of investigation upon the thyreotrophic hormone, owing to two important discoveries

made at this time, namely, that thyreoid stimulation could be obtained independently of gonadotrophic and growth effects[54] and that pituitary extracts could induce thyreoid hyperplasia not only in amphibia but in mammals.[15][16][164][165] Crew and Wiesner[54] found that the metamorphic factor was more resistant to heat than the gonadotrophic or the growth factor, and this property was used to obtain thyreotrophic extracts free of gonadotrophic and growth-promoting activities. They also point out that the thyreotrophic extracts used by Uhlenhuth and Schwartzbach[299] must have had little, if any, growth-stimulating or gonadotrophic activity, as they were heated for a sufficient length of time to destroy these properties.

Aron[15][16] was the first to demonstrate the effect of pituitary extracts upon the mammalian (guinea-pig) thyreoid. Aron's work has been confirmed by Loeb and Bassett[164][165] and also by Loeb, Bassett and Friedman,[166] as well as by numerous other workers; and the changes in the thyreoid which he described have formed a basis of a great deal of subsequent research, providing as they do a test by means of which the thyreotrophic activity of extracts and body fluids and tissues can be determined. For convenience, the morphological changes in the thyreoid following the administration of thyreotropic extracts may be referred to as "Aron's reaction", and they are of such importance that they call for description in detail.

Morphological Changes in the Guinea-Pig's Thyreoid (Aron's Reaction).

The changes begin in the centre of the gland and spread towards the periphery. Even in the normal resting gland of the young guinea-pig the central portions may show apparent slight activity, as indicated by the presence of cuboidal epithelium and partial resorption, with imperfect staining of colloid, although the peripheral follicles appear to be quite inactive.[39][189][51] It is therefore desirable in examining sections to choose a portion midway between the centre and the periphery. The following stages of activity may be recognized.

1. Stage "–" or resting phase. The epithelium is flattened with spindle-shaped pycnotic nuclei; the follicles are large, fairly uniform in size and filled with colloid which stains deeply and uniformly (Figure I).

2. Stage "+", commencing activity. The epithelium is still flattened. Slight vacuolation of colloid is seen at margins of the follicles (Figure II).

3. Stage "++", slight activity. The epithelium is cuboidal, the nuclei are slightly more rounded. Vacuolation of colloid is present, spreading from the margin towards the centre of the follicles (Figure III).

4. Stage "+++", definite activity. The epithelium is cubical, with rounded, less deeply staining nuclei. There is further absorption of colloid, which now stains poorly (Figure IV).

5. Stage "++++", marked activity. The epithelium is semi-columnar, the nuclei are rounded and situated towards the inner or the outer pole, they are poor in chromatin and exhibit mitotic figures. There is some hyperplasia, with infolding of the epithelium. Colloid stains poorly and shows vacuolation throughout the follicles (Figure V).

6. Stage "+++++", very marked activity. The epithelium is columnar, with round, poorly staining nuclei showing mitotic figures situated towards the inner or the outer pole. Marked hyperplasia is present, with infolding of epithelium, resulting in considerable diminution in the size together with distortion of the follicles. The hypertrophied cells contain minute granules scattered throughout the protoplasm, and also closely packed fine granules at the inner pole. The colloid shows vacuolation throughout the follicles, or it may form a thin poorly staining reticulum (Figure VI); later it may be broken up into granules and eventually it disappears (Figure VII). Hypertrophy of the Golgi apparatus has been reported.[218]

The condition of the epithelium forms the best guide to the stage of activity and is the main basis of the above classification. Slight activity may, however, sometimes be recognized by the appearance of marginal vacuolation of the colloid at a time when the epithelium is still flattened. On the other hand, glands are very occasionally encountered in which resorption of colloid fails to keep pace with hyperplasia of the epithelium,[99] and indeed there is no constant relationship between epithelial hyperplasia and colloid resorption. The above changes are accompanied by swelling and increased vascularity of the gland. Commencing microscopic changes may be observed within two[68] to twelve hours[136] of the administration of extracts.[2] If the administration be discontinued, the gland usually returns to normal within seven to eleven days. On the other hand, involution may begin to occur after an interval of a week or two, in spite of continued administration, owing to the development of resistance, a phenomenon which will be referred to later in detail.

Changes similar to those above described in the guinea-pig may be observed in other mammals, such as the rabbit,[17][21][264] rat,[21][9][103] mouse,[124][125][238] cat,[16][20][242][243] dog,[16][20][124][125][82][27] also in birds, including the duck,[251–255] the fowl,[81][213] the pigeon,[9] the sparrow,[204] and the chick.[273a][52]

Different species exhibit different degrees of susceptibility to the action of the hormone. Loeb[161] and Thurston[293] arranged them in the following order: mouse, rat, rabbit, cat, pigeon and guinea-pig, the last named being the most sensitive. Loeb[161] considers that this order is the inverse of that of the content of the pituitary in thyreotrophic hormone. Aron thought that the cat and rabbit were as susceptible as the guinea-pig, but this has not been confirmed, and there is general agreement that the guinea-pig is more susceptible than the rabbit.[264] Birds appear to be very sensitive, and Schockaert (*loco citato*) has obtained a 30% increase in the weight of the thyreoid of the young duck following the administration of thyreotrophic hormone. On the other hand, we have found

Macacus rhesus monkeys to be very resistant and sheep moderately susceptible.[296]

In general it would appear that those animals which rapidly develop resistance, such as the rabbit and the monkey, are the least susceptible, and the converse is true of those which less readily develop antithyreotrophic substances (see later) in the blood, such as guinea-pigs and birds.

The Aron reaction has been applied in a number of directions, such as the assay of thyreotrophic hormone, the detection and quantitative estimation of thyreotrophic activity in tissues and body fluids, the preparation of purified extracts and the study of the physiological action of the hormone and its role in pathological processes.

ASSAY OF THYREOTROPHIC HORMONE.

By Means of the Microscopic Changes in the Thyreoid.

Junkmann and Schoeller,[126] applying the Aron reaction, define the unit of activity as that amount of hormone which, injected daily for three days, causes recognizable hypertrophy of the epithelium and disappearance of colloid in the thyreoids of guinea-pigs of 100 to 150 grammes in weight. The test is carried out as follows:

> Two series of guinea-pigs of 150 grammes in weight are employed, one series being used for injection of hormone, the other as controls. All the animals are fed uniformly on moist bran together with a plentiful supply of green lucerne and kept warm at an even temperature. The series to be injected is divided into sub-groups of two or three animals, each sub-group receiving a different dose, subcutaneously. All the animals are killed on the fourth day; a careful *post mortem* examination is made in order to exclude the presence of infection, and the thyreoids are removed, sectioned and stained with hæmatoxylin and eosin. The microscopic changes in the thyreoid in the two series of animals are then compared. The threshold dose is that which produces semi-columnar epithelium, with marked resorption of colloid, the evidences of activity extending from the centre to the periphery of the gland. This degree of activity must be found in at least two animals of the sub-group receiving the same dose. Before a given dose can be taken as the minimum effective dose it is also necessary to ascertain that double or four times this dose will produce the maximal reaction.

Heyl[111][112] and Heyl and Laqueur[114] have proposed a modification of this method, using larger animals (weight 200 to 300 grammes), a shorter period of administration (two days) and injecting the hormone intraperitoneally instead of subcutaneously. They recognize six stages of activity (*p*, *q*, *r*, *s*, *t*, *u*), depending upon the extent of the changes in the central portion, the intermediate zone and the periphery of the gland, *p* being the absolute resting condition throughout the gland, *s* the critical stage of activity recognizable in the middle zone, and *u* the stage the maximal activity of the whole gland. The animals are divided into sub-groups of three, as in Junkmann and Schoeller's method. The unit of activity is taken as one-quarter of the total amount injected on two successive days, which in at least two out of three animals of a given sub-group will produce a degree of activity corresponding to stage *s*.

In this laboratory we have in general found it convenient to use Junkmann and Schoeller's method; but for greater sensitiveness and accuracy of dosage we prefer intraperitoneal to subcutaneous injection, and we take what I have above described as stage "+++" as the criterion of definite activity.

By Increase in Weight of the Thyreoid.

Rowlands and Parkes[235] take as the unit of activity the total quantity of hormone which, injected in equal portions for five days, causes the weight of the thyreoid of female guinea-pigs of 200 grammes in weight to be doubled, that is to say, to increase from about 31 milligrammes (the average normal) to 60 milligrammes. The number of animals used in each sub-group receiving a given dose is larger than in the preceding methods, namely, five to ten, the error involved varying with the number employed: 25% with five animals, 15% with ten, and 10% with twenty. Rowlands and Parkes have constructed a graph expressing the relation between hormone dose and gland weight, and from this the number of units can be read off when the weight of the glands is known. The unit of activity obtained by this method is approximately seven to thirteen times larger than the Junkmann-Schoeller unit.[134] Certain modifications of the Rowlands and Parkes method have recently been suggested by Junkmann and Loeser[135] which may possibly make for slightly increased accuracy.

The weight method has the advantage over methods based on microscopic changes in that the personal equation in weighing is less than that involved in assessing the degree of activity from the histological picture. On the other hand, it has the drawback that it is sometimes difficult to obtain uninjured glands completely free from connective tissue, and this may cause errors in weighing. A more serious difficulty is the lack of complete parallelism observed under certain conditions between the increase of the weight of the thyreoid and the degree of activity as judged by the microscopic changes. When one is dealing with pituitary substance, and particularly with purified thyreotrophic extracts of the gland, good correspondence between the changes in thyreoid weight and the microscopic picture may be obtained.[235][135] On the other hand, we have observed that the injection of urine and other body fluids is frequently followed by increase in the weight of the thyreoid while histologically the gland appears to be quiescent. Apparently contaminating substances may be present which influence thyreoid weight without inducing hyperplasia.[51][113][114] The reverse state of affairs, namely, the presence of a fully hyperplastic gland without corresponding increase in weight, may, although rarely, be encountered. The change in weight is an insufficiently delicate test for the recognition and assay of small quantities of hormone, such as may be met with in body fluids and tissues other than the pituitary, although it is quite suitable for the assay of potent pituitary preparations.

The Aron reaction is a much more delicate and possibly more reliable means of detecting and measuring the thyreotrophic activity of tissues and body fluids. In general we have found it to be the most useful, convenient and dependable method.

By Other Methods.

Attempts to assay the thyreotrophic hormone by means of the secondary functional changes which result from its action on the thyreoid have proved unreliable as well as difficult and time-consuming. The most important of these methods is that of Schoedel,[257] which consists in measuring the rise in oxygen consumption in male guinea-pigs of 300 to 500 grammes in weight, injected for three successive days with thyreotrophic hormone. The animals are kept at an external temperature of 30° C. for three weeks before the experiment. A curve of the rise of metabolism is constructed and from this the percentage rise is read off. As large doses have a relatively smaller effect than smaller doses, the curve, which is linear to begin with, tends to become flattened. It is therefore the effect of smaller doses coming within the limits of the straight part of the curve which are recorded as significant for the purposes of assay. The unit of activity is taken as a twentieth of the amount per kilogram of body weight injected on three successive days, necessary to raise the average oxygen consumption by 20%. This unit is approximately equivalent to the Junkmann-Schoeller unit—perhaps a little less.

Assay of the hormone by means of the changes in the level of thyreoid or blood iodine[284] is not only difficult and time-consuming, but moreover, the blood iodine relationship is possibly lacking in specificity.[114] Likewise, measurement of the size of the cells of the thyreoid or enumeration of mitoses do not commend themselves from the practical standpoint.

DISTRIBUTION OF THYREOTROPHIC HORMONE IN TISSUES AND BODY FLUIDS.

The Hypophysis.

The concentration of thyreotrophic hormone in the pituitary gland varies in different animal species,[234] the highest concentration being found in the rat (4,000 to 8,000 Junkmann-Schoeller units per gramme of dried anterior lobe[136][161]) and after this the sheep (1,000 units[136]), the ox (250 to 500 units[136][257]), the pig,[173] horse,[173] man (Müller, Eitel and Loeser[208]) and cat (Schittenhelm and Eisler[244][245]), in approximately that order. On the other hand, Rowlands[234] arranges species in the following order: dog, pig, cow, sheep, horse, the pituitary gland of the last named having the lowest content of thyreotrophic hormone. Müller, Eitel and Loeser[208] state that in the human hypophysis wide variations in the content of thyreotrophic hormone are met with, independent of age, the highest values being obtained in tuberculosis and other infections.

Other Tissues and Body Fluids.

Aron[19][20][22] and Aron and Klein[24] reported that the intraperitoneal injection of normal blood or urine in doses of 15 cubic centimetres causes hyperplasia of the central portions of the guinea-pig thyreoid, together with an increase in the weight of the gland, comparable with that induced by one to three milligrammes of fresh pituitary anterior lobes given at a single injection. The concentration of the hormone in the blood was said to be greater than in the urine and Van Caulaert[40] believed that there was a threshold for the excretion of the thyreotrophic hormone by the kidneys. Nielsen,[212] using the rabbit as a test animal, stated that intravenous injection of urine causes hyperplasia of the thyreoid in some conditions, while in others, including Graves's disease, it causes an increase in colloid with atrophy of epithelium. Fellinger,[76][77] using a special method of extraction, claims to have detected the presence of thyreotrophic hormone in serum.

All the above authors report negative results for both blood and urine in Graves's disease; but Giedosz, using the rabbit as a test animal,[84] obtained positive results with urine, not only in Graves's disease but in various other diseases.

Thyreotrophic hormone has been reported to be present in the cerebro-spinal fluid of the cat, dog[244] and man.[40] Trikojus and I have not so far encountered any thyreotrophic activity in the cerebro-spinal fluid of patients, removed by ventricular puncture for diagnostic purposes in cases of intracranial disease. Schittenhelm and Eisler[245] find that the hormone does not pass through the placenta and is not excreted in the milk.

Hellwig,[102] using the rabbit, claims to have demonstrated the presence of thyreotrophic hormone in the urine of pregnant women; but this is denied by Guyénot, Ponse and Dottrens,[99] who employed the guinea-pig as test object.

As regards the tissues, Schittenhelm and Eisler[244] report that the hormone is present in the mid-brain but not in other parts of the central nervous system. Various authors, including Sturm and Schoening, also claim to have demonstrated its presence in the suprarenal,[111][287] ovary, pancreas and spleen;[287][288] but Aron[20] states that testicles, kidneys, muscles and placenta induce no appreciable reaction in the guinea-pig's thyreoid.

The above results of Aron and his co-workers have been criticized by other investigators[146-149][39] on the ground that the thyreoids of untreated guinea-pigs of 200 grammes in weight frequently show activity, especially towards the centre; and, using metabolism estimations to check the histological reaction in suitable animals, they have been unable to find evidence of the presence of thyreotrophic hormone in normal blood and urine. (See also McGinty and McCullough.[189]) Krogh and Okkels[147-149] even failed to demonstrate thyreotrophic hormone in the urine after the injection of hormone into the animal; but this is contrary to the results obtained by Loeser,[173] who found substantial amounts in the urine after intravenous injection. However, Loeser[173] could find no appreciable amount of hormone in normal blood and urine, although it was possible to demonstrate

its presence in the blood of thyreoidectomized animals. As regards other organs, Junkmann[134] points out that the results of Sturm and his co-workers are doubtful because doses several times above the threshold effective dose were sometimes found to be ineffective.

Schockaert's experiments upon the action of casein on the thyreoid would suggest that some of the effects of tissue extracts may be non-specific.[255]

It may be concluded from the above that it is extremely doubtful whether thyreotrophic hormone is present in appreciable amounts in the normal body fluids and tissues outside the hypophysis.

PURIFICATION OF THYREOTROPHIC HORMONE.

As already mentioned, the earlier experiments on the action of the thyreotrophic hormone were made with grafts of pituitary glands or injections of crude emulsions of pituitary substance. Later, simple acid or alkaline extracts of anterior pituitary substance were employed (for example, Loeb and Bassett[164-166]); but with the introduction of a suitable method of assay it became possible to undertake methodically the purification of the hormone by determining quantitatively the activity of different fractions obtained by means of various solvents and precipitants. In this way potent extracts have been obtained by various workers.[170][171][136][61][149][10][235-97][154] In nearly all methods the initial stage of extraction is carried out by means of either acid, alkaline or neutral aqueous media. Alkali extracts a greater amount of hormone than acid, but causes greater contamination with protein, rendering subsequent purification more difficult. Further purification usually involves precipitation with alcohol or acetone, with or without preliminary removal of protein, followed by treatment with methanol[170][171] or 50% pyridine.[235] Anderson and Collip[10] employ fractional precipitation with ammonium sulphate, alcohol and acetone. Lambie and Trikojus[154] have described a rapid method of recovering the hormone from aqueous extracts by precipitating first with tungstic acid followed by reprecipitation with benzoic acid after preliminary removal of most of the protein with salicylsulphonic acid in dilute solution. Concentration by evaporation is eliminated and the use of organic solvents reduced to a minimum.

The extracts obtained by the methods of Junkmann and Schoeller and Lambie and Trikojus have on an average a potency of about 10 to 20 Junkmann-Schoeller units per milligramme. It is possible by further purification to obtain much more potent products; but this involves great loss of material. Junkmann[134] mentions that some of the purest preparations have a potency of 120 units per milligramme, while Dingermasse,[112] using a method similar to that of Junkmann and Schoeller, claims to have obtained a product having a potency of 80 to 120 units per milligramme. A stage of purification is now being reached at which it is possible to obtain products having an activity approaching that of other hormones which have been isolated in a pure state.

Junkmann and Schoeller's preparation is free from gonadotrophic, growth and lactogenic activities, whilst ours is free from the first named, but has not so far been tested for growth and lactogenic activities. Both preparations contain a trace of melanophore hormone.

Purified extracts such as the above are suitable not only for animal experiments, but for parenteral administration to the human subject.

PHYSICAL AND CHEMICAL PROPERTIES OF THYREOTROPHIC HORMONE.

Appearance.

The highly purified dried product appears as a white amorphous powder.

Solubility.

The purified extract is readily soluble in water and dilute acids and alkalis; also in watery methyl and ethyl alcohol and acetone, especially in acid solution. It is insoluble in concentrated organic lipoid solvents, such as ether, absolute alcohol, chloroform, acetone, pyridine and pentachlorethane;[136][134] but we have found that under certain conditions the hormone can remain in solution in 99% acetone.[154]

Precipitation.

Most of the contaminating proteins can be removed from crude extracts by iso-electric precipitation of aqueous suspensions at pH 5·0, and the hormone can be precipitated from the filtrate by the addition of three volumes of alcohol or saturation with ammonium sulphate.[46]

The hormone is precipitated by the salts of heavy metals and other protein precipitants, such as picric acid, picrolonic acid, trichloracetic acid, flavianic acid, phosphotungstic acid, mercuric chloride and silver nitrate.

Crew and Wiesner,[54] in their work on thyreotrophic hormone, used salicylsulphonic acid to precipitate most of the proteins,[1] but found that the filtrate contained the metamorphic factor. Later, Oehme, Paal and Kleine[214] reported that salicylsulphonic acid precipitated the factor responsible for hyperplasia of the guinea-pig's thyreoid and for stimulation of metabolism, while the filtrate still contained the metamorphic factor and also the factor capable of giving the acetonitrile (Reid Hunt) reaction. With regard to the latter, the variations which occur in the toxicity of acetonitrile to white mice render it doubtful whether great reliance can be placed upon this test.[34]

Junkmann and Schoeller[136] find that the purer the preparation, the less readily is the hormone brought down by protein precipitants.

Filtration.

Oehme, Paal and Kleine[214] reported that ultrafiltration, like precipitation with salicylsulphonic acid, removes the Aron reaction-producing and metabolism-stimulating factors, while ultra-filtrates

[1] Personal communication.

still contain the factors responsible for metamorphosis and the Reid Hunt reaction.[136] Anselmino and Hoffmann[13] and Loeser[173] state that the hormone producing hyperplasia in the guinea-pig's thyreoid does not filter through collodion membranes impermeable to protein, as shown by testing the filtrate with salicylsulphonic acid. It is clear, however, that a more careful study of the diffusibility of the hormone through membranes of graded permeability is called for. Recently, Collip[46] has reported that he and Denstedt, using the method of electrodialysis, found that the hormone has evidently a molecule of small size, although probably protein in nature, and that it is capable of passing through both collodion and fish bladder membranes. The fact that the hormone can be demonstrated in the urine after it has been injected intravenously[173] would also suggest that the molecule is sufficiently small to exceed the threshold of permeability of the renal glomeruli, corresponding to molecular weight of 68,000 or less, and therefore at least as small as that of hæmoglobin. It is, of course, possible that excess of extract from a foreign source injected intravenously may effect the permeability of the glomerular filter.

Adsorption.

The active principle is readily adsorbed by colloidal iron, especially in alkaline solution and by animal charcoal.[214][136] Kaolin is a somewhat less effective adsorbent.[136]

Stability.

In the completely dry state the hormone is very stable, extracts retaining their potency almost unchanged for at least a year.[170][171][136][134] On the other hand, in the presence of moisture or in watery solution (especially alkaline) its activity rapidly deteriorates.[170][171][136] Junkmann and Schoeller[136] find that potent extracts lose their potency in solution within three months when kept in a refrigerator.

Loeser[173] reported that the stability of aqueous solutions at room temperature is greatest at pH 5 and pH 9-10; but Junkmann and Schoeller[136] could find no such marked influence of pH upon stability at ordinary temperatures.

Resistance to Heat.

Crew and Wiesner[54] reported that the metamorphic factor is thermostable, and this was confirmed by Spaul,[281] Krichesky,[145] and Uhlenhuth and Schwartzbach.[302]

Oehme and Paal,[214] and Oehme, Paal and Kleine[214] found that the metamorphic and Reid Hunt reaction-producing factors found in ultrafiltrates were thermostable, but that the non-ultrafiltrable fraction giving the Aron reaction was thermolabile. Janssen and Loeser[131] and Loeser[170][171] likewise reported that the factor responsible for the Aron reaction is thermolabile, while Junkmann and Schoeller[136] and Junkmann[134] stated that it was almost completely destroyed by heating to 60° C. and absolutely destroyed by boiling for a short time. These discrepancies regarding resistance to heat with reference to the metamorphic and mammalian thyreoid-stimulating factors raised the possibility that there might be two distinct hormones acting upon the thyreoid.[134][154] Recent evidence, however, goes to show that highly purified preparations of thyreotrophic hormone are thermostable, even those giving the Aron reaction. Thus Lambie and Trikojus[154] have shown that although heating in 0·5% acetic acid for half an hour at 100° C. caused some loss of potency, the hormone was not completely destroyed; and Trikojus and Ellis[295] have found that even after boiling for one hour in neutral solution some activity is still retained. Collip[46] likewise finds that although boiling causes some loss of potency at all hydrogen ion concentrations the hormone exhibits great stability between pH 3 and pH 5, but is more rapidly destroyed by boiling at hydrogen ion concentrations above and below this range.

Resistance to Enzyme Action.

The hormone is destroyed by pepsin and trypsin, and this applies to both the metamorphic[281] and Aron reaction-producing[46] activities.

Chemical Nature.

The available evidence points to the conclusion that the hormone, if not itself a protein, is at all events very closely bound to protein. If a protein, it has probably a relatively low molecular weight, as suggested by its diffusibility. Purified extracts give the protein colour reactions, and the active principle is precipitated by protein precipitants.[136][134]

The destruction of the hormone by proteolytic enzymes and its apparent antigenic properties (see later) also point to its being of protein nature. The hormone has not yet been obtained in a sufficiently pure state to enable a satisfactory element analysis to be made or to determine its empirical formula; but the purest preparations contain carbon, hydrogen, oxygen, nitrogen and sulphur. It is apparently rich in oxidized sulphur, the sulphur content going parallel with physiological activity.[134]

PHYSIOLOGICAL ACTION OF THYREOTROPHIC HORMONE.

Owing probably to its destruction by proteolytic enzymes and possibly also to imperfect absorption, the hormone is inactive when given by the mouth; therefore, for purposes of physiological investigation, it has to be administered parenterally.

Mode of Action on Thyreoid.

The morphological changes in the thyreoid which follow the administration of thyreotrophic hormone have already been described and the question now to be discussed is that of the mode of action of the hormone upon the gland. There is every reason to believe that the action is a direct one, independent of the central nervous system. The following evidence may be adduced in support of this conclusion.

1. Excision of the superior cervical ganglion or of the stellate ganglion or even of the entire cervical sympathetic does not affect the action.[23][144][64][222]

2. The same morphological changes as those which occur in the intact animal are observed when the whole gland is removed from the body and perfused in the apparatus devised by Lindbergh.[216]

3. These changes also occur when extract is added to excised portions of glands placed in the Warburg apparatus for the determination of tissue metabolism.[65][220][58]

4. Finally, they are observed in fragments of thyreoid gland implanted under the skin of treated animals.[64][197][116][124][270] Sunder-Plasmann[288] and Gottdenker[87] claim that certain drugs, such as atropine and ergotamine, inhibit the action of thyreotrophic hormone, thus suggesting that the autonomic nerve endings may be involved in its action; but these results have not been confirmed.[140][65] Apart from the morphological changes which occur in the thyreoid, two classes of effect may be observed as the result of the administration of the thyreotrophic hormone: actions dependent upon the integrity of the thyreoid and actions independent of the thyreoid.

Effects Dependent upon the Thyreoid and Due to Increased Functional Activity of the Gland.

Effects dependent upon the thyreoid and due to increased functional activity of the gland are, of course, abolished by thyreoidectomy.

Passage of Thyreoid Secretion into the Blood.

If the morphological changes in the thyreoid are accompanied by increased secretory activity, it is to be anticipated that evidence of this would be obtained by a study of iodine metabolism and of the thyroxine content of the blood. Experiment demonstrates that this is the case.

Iodine Metabolism.—The administration of thyreotrophic hormone is followed by a diminution in the total and protein-bound iodine of the thyreoid and simultaneously an increase of these in the blood and increased elimination of iodine in the urine.[169][131][90][126][127][256][81][42][43][160][161][262]

Thyroxine Secretion.—While the study of iodine metabolism provides an index of thyroxine secretion, more direct evidence of this may be obtained by means of biological assay of the thyroxine content of the thyreoid gland and blood. Two methods are available, namely, the effect upon the metamorphosis of amphibia and the acetonitrile test (Reid Hunt reaction), that is to say, the property possessed by thyroxine of protecting white mice against the toxic action of acetonitrile. By these means it has been found that the administration of thyreotrophic hormone causes a decrease in the quantity of active principle in the thyreoid and an increase in the amount present in the blood.[91][242][136][214][215] These experiments indicate that the effect of thyreotrophic hormone is to stimulate the thyreoid to increased secretory activity, but there is no evidence that it has any effect upon the synthesis of thyroxine.

Effects Attributable to the Action of Thyreoid Secretion.

The following effects are so similar to those obtained by the administration of thyreoid substance or thyroxine that it is reasonable to suppose that they are due to thyreoid secretion.

Rise in Basal Metabolism and Oxygen Consumption.—A rise in basal metabolism and oxygen consumption has been demonstrated in many species, including guinea-pigs,[158][159][303][9][83][266][267] rats[10] and man,[242][243][69][214] the results in mammals being in accord with those previously observed by Uhlenhuth in amphibia (*vide ante*). In rats the rise begins on the first day of administration and reaches a maximum in six to fourteen days; thereafter the metabolism declines in spite of the continued injection of extract, reaching the normal level in one to three weeks or even going below it. In this species the maximum increase amounts to about 26% above the basal level,[10] while in guinea-pigs the rise amounts to 26% to 60%.[83]

Rise of Temperature.—In some species the increase in metabolism is accompanied by a rise of temperature. For example, in the guinea-pig Friedgood[83] observed a significant rise of about 1° F. in the rectal temperature. Schittenhelm and Eisler[242][243] report a slight rise of temperature in man.

Loss of Weight.—There appears to be no constant relationship between loss of weight and increase in energy metabolism.[83][181-183] In the guinea-pig the basal weight shows a decrease of 6% to 27% below the normal.[83]

Heart and Circulation.—The rise in energy metabolism is accompanied by the following changes: (i) Tachycardia, which may be accompanied by palpitation in man.[242][243][291][100][172][83] No significant change in the electrocardiogram[68] has been recorded. (ii) Increased cardiac output and stroke volume;[133] but in spite of this, (iii) a diminution in the mechanical efficiency (that is, the energy consumed for a given amount of work done) of the heart; and (iv) a fall in the adenylpyrophosphoric acid content of the heart muscle.[28] The last-named change is of interest in view of the fundamental importance of adenylpyrophosphoric acid in muscular contraction.[188] This substance is the primary source of energy in muscular contraction and yields heat by anaerobic splitting off of phosphorus and ammonia. A similar fall in the adenylpyrophosphoric acid of the heart muscle occurs after the administration of thyroxine, and perhaps it may throw some light upon the cause of cardiac dilatation and failure in thyreotoxicosis. In accord with the transitory nature of the other changes due to the thyreotrophic hormone upon the thyreoid, the fall in adenylpyrophosphoric acid content of the heart passes off about the eighth day.

Nervous System.—The effects present some resemblance to those observed in thyreotoxicosis in man. (i) Appetite. Some workers have reported an increase in appetite accompanying the rise in metabolism.[69][172] In guinea-pigs, however, the

administration of large doses of thyreotrophic hormone causes a loss of appetite during the first week, probably owing to the development of thyreotoxicosis; but this wears off with the development of resistance.[83] (ii) Excitability. Guinea-pigs first show decreased activity, but this may be followed after a few days by marked excitability.[100][83] (iii) In man tremor has been observed.[242][243][69]

Skin.—In man the administration of the hormone causes increased warmth and moisture of the skin. In guinea-pigs some falling out of fur, probably the result of thyreotoxicosis, is reported by Friedgood.[85]

Carbohydrate Metabolism.—Liver glycogen: From what is already known regarding the effect of thyreoid extract on carbohydrate metabolism it is to be anticipated that the thyreotrophic hormone would cause a fall in the glycogen content of the liver. This has been found to be the case.[67][68][119][174][180][243][104][73] Unlike the preceding changes, this fall begins only after a latent period of four days; but in this respect the action of thyreotrophic hormone merely corresponds to that of thyroxine. The maximum fall is obtained in from seven to ten days, and thereafter the glycogen content of the liver begins to rise again. Schneider and Widman[248] and Hanke and Widman[104] point out that the fall in liver glycogen is not accompanied by fatty infiltration.

Muscle glycogen: The muscle glycogen is little if at all affected by the administration of thyreotrophic hormone.[67][68]

Blood sugar: The blood sugar likewise is little changed, although Rothschild and Staub[233] report a 200% rise after intravenous injection of large quantities of extract over a period of seven days; but this effect may have been due to the presence of diabetogenic hormone in the extract. That some lowering of carbohydrate tolerance occurs is suggested by the fact that glycosuria may occur in man after the administration of 100 grammes of glucose in individuals treated with daily injections of 600 units of thyreotrophic hormone.[67][68]

Protein Metabolism.—Just as thyreoid administration causes a rise in endogenous metabolism, so does the injection of thyreotrophic hormone. An increased output of urea and creatinine has been observed, and creatine may appear in the urine.[10][233][241]

Water and Salt Metabolism.—There is an increased elimination of water and salt in the urine, an effect partly secondary to the changes in protein metabolism which give rise to metabolites having a diuretic action.[233]

Mineral Metabolism.—The mineral metabolism has been incompletely investigated; but it has been shown by Pugsley and Anderson[225] that the administration of thyreotrophic hormone causes an increased excretion of calcium, especially in the fæces, similar to that which results from the administration of thyreoid.[226] Schneider and Widman[248] and Hanke and Widman[104] find that thyreotrophic hormone produces a fall in the sodium of the liver and of the blood without any accompanying fall of calcium or chloride. (See also Eggs.[63])

Adrenal Hypertrophy.—Adrenal hypertrophy is here provisionally classed among the effects of thyreotrophic hormone caused indirectly by increased thyreoid activity. There is, however, considerable doubt as to whether this is justified in view of the uncertainty which exists in regard to the exact role, if any, of the thyreoid or of the thyreotrophic hormone in the causation of adrenal hypertrophy. On the one hand, the following facts recorded by Loeser[172][174] seem to point to the importance of the thyreoid and of thyreotrophic hormone. (i) Adrenal hypertrophy occurs after the administration of pituitary extracts rich in thyreotrophic hormone, the hypertrophy affecting the cortical portion of the adrenals, and the adrenaline content of the glands remaining unaltered. (ii) This effect is dependent upon the integrity of the thyreoid, since it does not occur after thyreoidectomy. (iii) Thyroxine produces adrenal hypertrophy (compare Herring,[108] Hoskins,[123] Iscovisco, Hewitt,[115] Loeser, Ruland and Trikojus regarding effect of thyroxine-O-methyl ether, 1938). On the other hand, Collip[45][46] claims to have obtained pituitary extracts which have a corticotrophic action without possessing any thyreotrophic activity; indeed, Reiss and Peter[228] have brought forward evidence to show that corticotrophic extracts may actually depress the thyreoid, as shown by the lowering of epithelium in the thyreoid and a fall in blood iodine, the action of such extracts being apparently antagonistic to that of thyreotrophic hormone. This suggests that there may be an independent hormone, possibly closely related to the thyreotrophic hormone, which is responsible for the corticotrophic effect, and that this hormone may have been present along with thyreotrophic hormone in Loeser's extract. If, however, adrenal hypertrophy does not occur in the absence of the thyreoid, a possible interpretation of the facts is that thyroxine sensitizes the adrenals to the action of the corticotrophic hormone; but before this conclusion is reached evidence is required to show that Collip's corticotrophic extract can produce adrenal hypertrophy in thyreoidectomized animals. Adrenal hypertrophy continues to develop as a result of prolonged administration of pituitary extract, even after the thyreoid gland has undergone secondary involution. This would seem to point to adrenal hypertrophy being an effect largely independent of the thyreoid. Indeed, the possibility exists that the involution of the thyreoid after prolonged administration of thyreotrophic hormone may be in some way bound up with adrenal hypertrophy and the action of corticotrophic hormone.

Effect Independent of Thyreoid.

Exophthalmos.

The only effect of anterior pituitary extracts supposedly attributable to the action of thyreotrophic hormone which has been shown to be independent of the thyreoid is exophthalmos.

Whether this condition is really due to thyreotrophic hormone or to some other substance contained in pituitary extracts may be regarded as an open question; but in the absence of proof of the existence of such an independent factor economy of hypothesis compels us to assume provisionally that it is an effect of the thyreotrophic hormone. In this connexion, however, it may be pointed out that exophthalmos, like adrenal hypertrophy, persists and increases as a result of prolonged treatment with pituitary extracts in spite of the appearance in the blood of substances antagonistic to the action of thyreotrophic hormone in amounts sufficient to neutralize all those effects which have been described as secondary to increased thyreoid activity.

Exophthalmos has been observed in ducks[253][254] and guinea-pigs.[168][83][221] In this laboratory attempts to produce it in *Macacus rhesus* monkeys by prolonged administration of potent extracts of thyreotrophic hormone have so far proved unsuccessful. The mode of production of exophthalmos will be discussed more fully in connexion with clinical syndromes; but it may be stated here that its independence of the thyreoid is shown by the fact that it can be produced by the prolonged administration of thyreotrophic hormone in the absence of the thyreoid. Indeed, it occurs more readily in the thyreoidectomized than in the intact animal. Even in the intact animal it appears to be most marked at a time when the thyreoid gland is undergoing involution owing to the development of resistance.[83] In guinea-pigs, whether thyreoidectomized or intact, we have been unable by means of prolonged injection of our purified and highly potent extracts to obtain definite and persistent exophthalmos with the regularity claimed by other experimenters; and we feel that there is some justification for scepticism in regard to the ease with which it can be produced, in view of the fact that the criteria of exophthalmos are frequently unconvincing and its measurement is insufficiently objective.

Resistance.

Development of Resistance.

In the preceding section several references have been made to the fact that when thyreotrophic hormone is administered continuously it begins after a few days to lose certain of its effects, that is to say, the animal becomes resistant to its action. This phenomenon is observed only in respect of the changes in the thyreoid gland and the secondary effects dependent upon the thyreoid; but it does not develop in relation to exophthalmos, nor does it affect adrenal hypertrophy. The morphological changes in the thyreoid associated with increased activity of the gland, together with all the secondary changes dependent upon this hyperactivity, attain their maximum in the guinea-pig and rat as a rule about the seventh to the twelfth day of administration; there is then a gradual decline of all these towards the normal, which may be reached in about two to four weeks, and thereafter a subnormal phase associated with hyperinvolution of the thyreoid may supervene.[136][162][83][49][10][158][266][267] Only in the case of the fall in liver glycogen is there a delay in the onset of the changes referred to.[67][68][172][179] As regards the thyreoid, involution associated with the development of resistance is marked by a gradual return of the epithelium to the flattened shape and the reappearance of colloid. A noteworthy feature is the appearance of interstitial lymphoid hyperplasia and fibrosis, conditions which are recognized in human pathology[194][195] as characteristic of involution states of the thyreoid (see Figure IX).

Ætiology of Resistance.

Two factors appear to be involved in the ætiology of resistance, namely: (i) the appearance of neutralizing substances in the blood, and (ii) the inhibitory effect of thyreoid secretion upon the pituitary—that is to say, the endogenous regulation of hormone balance.[180]

It will be evident from what follows that there is no reason to suppose that resistance is merely a manifestation of exhaustion of the thyreoid or of the development of tolerance.

Neutralizing Substances.—Evidences of their existence: Evidence of the existence of neutralizing substances in the blood is based upon the following observations:

1. The blood of rats treated for several weeks with thyreotrophic hormone causes a fall in the basal metabolism when injected into normal rats and prevents the rise in metabolism induced by the injection of thyreotrophic hormone; but it has no effect upon the rise of metabolism due to administration of thyroxine.[47][48]

2. The antithyreotrophic activity of blood and other body fluids can be demonstrated by injecting guinea-pigs intraperitoneally daily with a given quantity of the fluid in question, and on the fifth and sixth days administering simultaneously a known dose of thyreotrophic hormone. The animals are killed on the seventh day and their thyreoids are examined and compared with those of controls. In this way it is possible to determine the number of units of thyreotrophic hormone neutralized by a given amount of material. Besides being a qualitative test of the presence of neutralizing substances, this constitutes a useful method of assay.[106][70]

3. That the immunity is not cellular is shown by the fact that the thyreoid of the rabbit rendered resistant by repeated injections of thyreotrophic hormone, when perfused in the Lindbergh apparatus, can be activated by the addition of thyreotrophic hormone to the perfusion fluid.[216][217] Collip and Anderson have ascribed the neutralizing power of blood to the presence of what they call the "antithyreotrophic hormone". There are, however, objections to the use of such a term. In the first place it is not certain that the neutralizing activity is due to a single substance, and secondly, there is no proof that it is due to a hormone; that is to say, if we are to confine the use of the word hormone to the secretion of an endocrine gland. The removal

of any one of the endocrine glands, with the possible exception of the thyreoid, does not prevent the development of antithyreotrophic activity[70][68][71][72][178] and the only possibility of the neutralizing substance being derived from an endocrine gland would be its introduction with the pituitary extract used for immunization and its accumulation in the treated animal. It may be mentioned here that Gottdenker has brought forward evidence[87] to show that the posterior lobe of the pituitary contains a substance which antagonizes thyreotrophic hormone. In the meantime it would seem better to use terms such as antithyreotrophic protective or neutralizing substances,[162][163][246] which do not commit one to any hypothesis regarding the origin of these bodies.

Nature of neutralizing substances: The neutralizing substances bear certain resemblances to antibodies.[105] Thus they are precipitated in the globulin fraction of serum, they are destroyed at about the same temperature, and they are destroyed by proteolytic enzymes, which suggests that they are proteins. Further, they are hormone specific; that is to say, they neutralize only the thyreotrophic hormone and not, so far as is known, any of the other pituitary hormones,[47][48] so that they would appear not to be antibodies to the pituitary proteins apart from thyreotrophic hormone. They are not, however, quite species specific, but, as is common in immunity reactions, they exhibit a good deal of group immunity.[202][277] For example, if thyreotrophic hormone from ox pituitary is used to immunize a sheep, the antibodies which appear in the sheep's blood will not only neutralize ox thyreotrophic hormone, but also a sheep's thyreotrophic hormone, the guinea-pig being used as the test animal for measuring thyreotrophic power of the serum against the hormone as above described.[177][178] In this connexion, Young[307] has made the interesting observation that antiserum to anterior pituitary extracts containing prolactin and diabetogenic hormone, but having no detectable thyreotrophic action, showed substantial antithyreotrophic activity. This may mean that either prolactin or the diabetogenic hormone can excite the production of the antithyreotrophic principle or that the antisubstances to which these hormones give rise are sufficiently similar to the antibodies to thyreotrophic hormone as to exhibit group immunity.

In spite of these apparent resemblances to antibodies, there are certain respects in which the antithyreotrophic neutralizing substances present in the blood differ in their properties and reactions from true antibodies. Thus it has not been possible to obtain the neutralization of thyreotrophic hormone by antiserum when these are incubated together *in vitro*.[177][178] Attempts to demonstrate neutralization in perfusion experiments have also failed, for when the thyreoid gland is perfused with the blood from a refractory animal the addition of thyreotrophic hormone to the perfusion fluid has the usual stimulating action upon the gland.[216][217] Eitel and Loeser[71][72] have also drawn attention to an observation which is difficult to reconcile with the antibody theory. They report a failure to raise the neutralizing titre of the blood in animals which have been deprived of their thyreoid; but the administration of thyroxine to thyreoidectomized animals will restore the capacity to increase the titre, although thyroxine itself has no power to stimulate the production of neutralizing substances.

Perhaps these conflicting results may be due to there being more than one kind of neutralizing substance present in the blood, the effect produced being dependent upon the way in which the blood is treated (for example, with solvents, precipitants) prior to being tested for antithyreotrophic activity.

That all the neutralizing substances are not antibodies is rendered probable by the fact that protective substances are to be found even in normal blood.[70][71][177][178][265][236][106][271] The neutralizing power of normal blood varies in different species, and, according to their neutralizing activity, these may be arranged in the following order: sheep, horse, rat, cattle, goat and guinea-pig, the last named being the least active.[236][177][178]

While it is improbable that an animal would develop true antibodies to its own hormones, it has not yet been definitely settled whether it is possible to raise the antithyreotrophic activity of the blood of an animal in response to treatment with thyreotrophic hormone from the same species. Anderson and Evans[11] report that they have succeeded in doing so in the rat; and if this is confirmed it will be another point difficult to reconcile with the antibody theory. The existence in normal blood of neutralizing substance to hormones has no real analogy with the existence in normal blood of true antibodies to bacteria or their toxins (for example, diphtheria antitoxin), for the latter are probably produced as a result of low-grade infection by foreign organisms and are not evolved endogenously in response to a stimulus provided by a normal constituent of the animal's own tissues. Loeser[181][182] mentions that antithyreotrophic extracts of normal sheep's blood, prepared according to the method of Loeser and Trikojus,[186][187], are active by the mouth. If this is confirmed, it would point to the antithyreotrophic substance present in the blood being different in nature from true antibodies. It has not been definitely shown that thyreotrophic activity can be demonstrated in extracts completely free from protein, but it is present in protein-poor filtrates after precipitation of serum proteins.[186][187]

Further work is required in order to determine whether or not there exist two (or more) kinds of antithyreotrophic protective substances and, if so, whether the titre of more than one variety can be raised by treatment with thyreotrophic extracts from the same or from different species. For the present, economy of hypothesis compels us to assume that there is only one substance of importance responsible for the antithyreotrophic activity of blood, that it is present in normal blood and can be increased in response to treatment with thyreotrophic hormone, at all events from a foreign source, and that if it is not a protein it is closely

bound to protein; the source of the substance is unknown.

Endogenous Regulation of Hormone Balance: Inhibition of Pituitary Secretion.—The influence of the thyreoid upon pituitary secretion is shown by the effects both of diminished and of increased thyreoid secretion.

A. Diminished thyreoid secretion causes increased pituitary activity. Thus Rogowitsch, as far back as 1889, showed that excision of the thyreoid leads to hypertrophy of the pituitary. This hypertrophy is accompanied by an increase in the content of thyreotrophic hormone in the pituitary.[308] It has also been shown that compensatory hypertrophy of the thyreoid remainder after removal of one half of the thyreoid depends upon the integrity of the pituitary.[138]

B. Increased thyreoid activity, on the other hand, causes diminished pituitary secretion. Thus it has been found that the administration of thyreoid extract or of thyroxine prevents pituitary hypertrophy in thyreoidectomized animals, diminishes the content of the pituitary in thyreotrophic hormone and inhibits the secretion of thyreotrophic hormone.[120][151][173] The evidence for the last-named action is that after the administration of thyroxine quantities of thyreotrophic hormone which normally produce thyreoid hypertrophy, remain below threshold. In view of the diminished content of the pituitary in thyreotrophic hormone this is interpreted to mean that the pituitary, under these conditions, does not contribute its normal quota of thyreotrophic hormone to the total amount supplied to the tissues. Another factor, however, may be an alteration in the reactivity of the thyreoid to thyreotrophic hormone as a result of the action of thyroxine.[184] Recent evidence[191] suggests that the administration of thyroxine may actually cause a reversal of the action of thyreotrophic hormone, as shown by the lowering of metabolism. This would point to there being something more involved than a mere inhibition of secretion.

Overcoming of Resistance; Production of Acute Thyreotoxicosis.

There are two ways of overcoming or avoiding the development of resistance, namely, by giving very large and especially increasing doses of thyreotrophic hormone, and secondly by breaking up the "hormone-antigen complex".

1. Excessive or crescendo dosage. The following experiment, designed by Loeser,[182-183] illustrates the crescendo method. Two series of animals, (*a*) and (*b*), are subjected to treatment with thyreotrophic hormone over a period of (up to) 14 days, the weight of the animals and the basal oxygen consumption being recorded. The total amount of thyreotrophic hormone administered over the whole period of the experiment was approximately the same in each series, namely, 1,700 J-S units. In series (*a*) the initial dose was small (20 units) and the final dose large (400 units), the dose being increased every third day. In series (*b*), on the other hand, the dose was uniform (120 units daily) throughout the experimental period. The animals of series (*b*) showed a transient rise in metabolism, which reached its maximum (+29% to +40%) about the seventh day, and thereafter the oxygen consumption showed marked fluctuations, which are interpreted by Loeser as the expression of attempts at endogenous regulation of hormone balance. All animals of the series survived. In contrast to those of series (*b*) the animals in series (*a*) exhibited a much greater rise in metabolism (maximum +56% to +83%) and a condition of acute thyreotoxicosis, resulting in the death of the animals, was produced. In some instances the metabolism continued to rise until death or the end of the experiment; in others death was preceded by a fall in metabolism. At *post mortem* examination the kidneys exhibited necrosis and fatty degeneration, and the liver was the seat of fatty degeneration and leucocytic infiltration—findings which have their parallel in fatal thyreoid crises in man.

Recently, Trikojus and Ellis[295] have found that the dose of thyreotrophic hormone is an important factor in determining the time taken for the recession of the morphological changes in the thyreoid.

2. Breaking up the "hormone antigenic complex". According to Werner,[305] breaking up of the "hormone antigenic complex" may be accomplished by the use of flavianic acid. The hormone flavianate is said to cause thyreoid hypertrophy, but not to excite the development of resistance. It is desirable that this work should be confirmed.

OSTEITIS FIBROSA CYSTICA GENERALISATA AND PARATHYREOID TUMOUR.

By JAMES F. HUGHES, M.D.,[1]

Austin Hospital for Cancer and Chronic Diseases, Melbourne.

. . . every year, such cases came to the important clinics and before the eyes of the busy clear-eyed practitioners; and then, unnoticed and not understood, they disappeared from view.

SUDHOFF.

THE above statement, originally applied to the first recognition on the Continent of thyreotoxicosis by Carl von Basedow in 1840, is extraordinarily applicable to the past and present history of the disease entity known as *osteitis fibrosa cystica generalisata* (von Recklinghausen). For years the clinical features and the pathological characteristics of this condition remained unknown. Even today its more precise ætiology is still obscure.

The reasons for this paper are several. In the first place the syndrome of *osteitis fibrosa cystica* and parathyreoid tumour is still a rarely recognized one—sufficiently rare indeed to attract the attention and interest of all those who are familiar with one of the most important and dramatic chapters in medical history. Secondly, the case to be described

[1] George Adlington Syme Research Scholar, Royal Australasian College of Surgeons.

presents many features of considerable clinical and pathological interest. The third reason for the discussion of this condition is the almost complete lack of any such work in Australian medical literature. This is of considerable importance, for diagnosis and treatment in uncommon diseases seem to depend very largely on the publication of locally occurring cases. Only two patients with generalized *osteitis fibrosa* with parathyreoid tumour have so far been reported as successfully treated in Australia; one was the patient of Dr. Ross (Geelong),[27] the other of Dr. Kilvington (Melbourne).[15]

The diagnosis of the condition and the subjection of such a patient to operation comprise one of the adventures of modern medicine. Should diagnosis and treatment fail, the patient is condemned to a progressive and inexorable decline, with an ultimate fatal termination. Too eager diagnosis and ill-balanced judgement on the other hand will result in a futile and even dangerous exploration of the neck, which can only produce discredit.

It is because of the paucity of locally reported cases, and in the hope that more of these patients will be recognized and restored to health, that this review of the world literature up to the beginning of 1938 has been made.

Historical.

Three distinct phases in the history of generalized *osteitis fibrosa* are recognizable. The first phase comprises the nineteenth century and the years preceding it, and terminates in the year 1891. During this period ideas regarding diseases of bone were remarkably confused. The reason for this is apparent, for, as Dawson and Struthers[5] remark as recently as 1923:

> The clinical picture of many of the osseous dystrophies is often far from clear, the diagnosis often equally difficult, and the pathological picture extremely varied.

Various inclusive terms were given to these conditions, the French referring to them as "osseous dystrophies", whilst German authors, following von Recklinghausen, used the term "rhachitic malacias". The first of these diseases to be recognized as a definite pathological entity was *osteitis deformans*, the recognition and description of which was accomplished by Sir James Paget in 1877.[24] For some time *osteitis fibrosa* was regarded as identical with *osteitis deformans*, as indicated by the term applied to it by von Recklinghausen: *"ostitis fibröse oder deformirende"*.[25] It was believed by many to be a juvenile form of that disease.

Osteitis fibrosa was first accurately described and named by von Recklinghausen in 1891 as part of a group of bone diseases about which he wrote as a contribution to the *Festschrift* in honour of the great German pathologist Virchow, on the occasion of the latter's eighty-first birthday. Its causation, however, remained unknown. The establishment of *osteitis fibrosa* as a disease entity marks the beginning of the second phase of its history, the stage of the development of our knowledge regarding its ætiology.

In 1904 Askanasy described a case of this disease which at autopsy was found to be associated with a tumour of the parathyreoid gland. This observation passed relatively unnoticed until 1907, when Erdheim[6] described three cases of softening of the bones associated with parathyreoid enlargement. The view which then arose was that the enlarged parathyreoid glands occurred as a compensatory phenomenon and were entirely secondary to the bone disease. Many other observations of bone disorder associated with parathyreoid enlargement followed. In 1915 Schlagenhaufer[26] came in contact with two cases of *osteitis fibrosa* in which parathyreoid tumours were found at autopsy, and was the first to suggest that perhaps the enlarged parathyreoids were the primary phenomenon, removal of which might cure the bony lesions. Weil,[32] in 1922, with the same idea in mind, administered radiotherapy to the neck in a case of generalized *osteitis fibrosa* and stated that remarkable benefit had resulted. In the same year Morton,[22] after an extensive review of the literature, suggested that in *osteitis fibrosa generalisata* there was a disturbance of calcium metabolism, and that this was analogous to the abnormal carbohydrate metabolism of *diabetes mellitus*. He thought that the blood calcium level might be higher than normal and that this would result in a loss of calcium in the urine.

In 1926, Collip,[4] after the isolation of the parathyreoid hormone, showed that its administration produced a rise in the blood calcium level. He thus demonstrated that the function of the parathyreoid was the regulation of the level of the blood calcium. In the same year Hannon, Shaw, McClellan and Du Bois[10] investigated a patient exhibiting general skeletal decalcification with a large cyst in the right femur, and found a high serum calcium level (15·3 milligrammes *per centum*) and a low serum phosphate level (1·4 milligrammes *per centum*). Later investigations of the same patient by Richardson, Aub and Bauer[26] showed that the urinary output of calcium and phosphorus on a standard diet was six to seven times greater than in a normal individual under the same conditions. They found that these metabolic changes were equivalent to those occurring in a normal individual after the administration of 100 units of parathormone daily. It was consequently concluded that the patient had hyperparathyreoidism.

In 1925 Hoffheinz had collected from the literature a large number of cases of *osteitis fibrosa* associated with parathyreoid enlargement, the latter still being regarded as compensatory in nature. In 1926 Mandl,[20] by reason of the prevailing viewpoint, treated a patient by grafting parathyreoid tissue. The patient, however, showed no improvement, and it was then decided to explore the neck, though no tumour could be felt. This was done and a parathyreoid tumour, 2·5 by 1·5 by 1·2 centimetres, was found and removed. The patient's bone pains rapidly disappeared, and considerable improvement was effected. Thus ended the second historical phase, with the establishment of the ætiological

relationship of parathyreoid enlargement to *osteitis fibrosa cystica generalisata*.

The third, or present, phase extends from 1925 up to the present day and consists in the consolidation and development of the discoveries so nobly summated by the work of Mandl. To Hunter[13] belongs the credit for the recognition of the syndrome in Britain, where many cases were described in the literature about this time, there being no knowledge of any effective method of treatment. Hunter established parathyreoidectomy as the treatment in these cases, and greatly elucidated many of the obscure aspects of the disease. In 1931 he reviewed the 22 cases in which operation had been performed up to that time.[3] Since then the number of reported cases in which surgery has been employed has increased considerably; by 1934 it had amounted to 115 since the case of Mandl.[9] By the beginning of 1936 the number had grown to 135, according to the careful review of Wilder and Howell.[33] Sixteen additional cases were reported during 1936, 18 during 1937, and 17 during 1938, making a total at the beginning of 1938 of 186. My own case may now be considered.

Report of Case.

The patient was a female, aged thirty-two years. Two and a half years ago she gradually developed aching pain in the left hip and began to limp on that leg. Two months after the onset of symptoms she slipped on the floor at home and fractured the neck of her left femur. She was admitted to the Royal Melbourne Hospital and a Whitman's plaster was applied. A radiograph taken ten weeks later revealed early union of the fracture, and she was therefore discharged from hospital. Three months afterwards a swelling was observed on the left hip. Radiographic examination revealed an appearance of the upper end of the left femur which was reported as "characteristic of malignancy", either primary (osteogenic sarcoma) or secondary (metastatic carcinoma). No primary tumour which could be held responsible for the latter could be found. Radiotherapy was ordered for the hip condition, and of this the patient had three courses of treatment. As a result of the therapy the swelling rapidly diminished in size, the bone recalcified, and the patient was discharged from hospital with the tumour almost gone. During her stay in hospital she passed a number of urinary calculi and said that she had had hæmaturia on and off for five years. Radiological examination of her kidneys revealed the shadows of calculi. Radiographic examination of the left scapula revealed "expansion, with areas of rarefaction scattered throughout the body and head. Appearances not typical of metastases." Skiagrams of the left femur revealed "marked sclerosis and increase in density". No definite changes were visible in the other bones. The provisional diagnosis of a malignant neoplasm of the femur was still retained.

Twelve months ago (approximately eighteen months after the onset) the patient fell and fractured the neck of her other femur. She was then sent to the Austin Hospital, as she was considered to be suffering from incurable cancer. X ray examination now showed not only the fracture but an expansion and cystic involvement of the proximal half of the right femur, with a similar appearance of the left femur (except for some localized sclerosis following the radiotherapy) (Figure I). The radiographs of the scapulæ now revealed expansion and multiple cysts (Figure II); those of the skull revealed extensive involvement with circular areas of bone destruction (Figure III). In the remainder of the skeleton evidence of generalized decalcification was found (Figure II). Shadows of calculi were present in the kidneys. At this time severe intractable headache was the patient's main complaint.

Biochemical investigations were now carried out and revealed a serum calcium level of 19 milligrammes *per centum* (the normal being 10 milligrammes *per centum*) and a serum phosphate level of 0·36 milligramme *per centum* (normal, three to five milligrammes *per centum*). The plasma phosphatase content was raised to ten units; the normal unit value estimated by the method used was six.

Metabolic studies, for example the determination of her calcium balance, were not performed.

The Wassermann test elicited no reaction, whilst renal function tests revealed a moderate impairment of renal efficiency.

It was now concluded that this patient must have generalized *osteitis fibrosa cystica*. No parathyreoid tumour could be palpated in the neck or revealed radiologically; but as this is possible only in a minority of cases, it did not affect the diagnosis.

On June 15, 1938, under nitrous oxide and oxygen anæsthesia, the neck was explored through a Kocher collar incision by Dr. Hugh Trumble. As the variability in situation of parathyreoid tumours is notorious, preparations had been made for an exploration not only of the neck but also of the upper part of the mediastinum if necessary.[1][2][12][23]

In this case the tumour was located at the posterior aspect of the lower pole of the right lobe of the thyreoid. It was enucleated and removed. A smaller nodule, found at the upper pole of the same lobe, was also excised. The left lobe of the thyreoid revealed no abnormality. The wound was then closed in the usual manner.

Post-operatively the patient's condition was satisfactory until the second day, when she became maniacal, with delusions of persecution. Calcium gluconate was administered and the nervous symptoms cleared up over the course of a week. They were regarded as being due to the sudden fall in the serum calcium content, resulting in hyperexcitability of the nervous system. Acute mania similarly complicated the case of Snapper.[29] No tetany was found in this patient. Her bone pains, especially her severe intractable headache, rapidly diminished in severity (in the course of a week) and soon completely disappeared. This is the usual finding in cases of *osteitis fibrosa* after successful parathyreoidectomy, and forms an important criterion of the accuracy of diagnosis and of treatment. After the operation there was a fall in the serum calcium level from the pre-operative 19 milligrammes *per centum* to 10 milligrammes *per centum*, which was accompanied by a reciprocal rise in the serum phosphate content. Her general health and feeling of well-being were rapidly restored.

Four months after operation this patient returned for review of her case and radiographic examination of her skeleton. An X ray examination revealed a considerable amount of recalcification affecting all her bones, although the cystic condition of her femora still persisted. The most pronounced changes were observed in the skull, where the obviously pathological appearance in the earlier films underwent rapid change towards normal. She felt much stronger and required sticks only as an occasional support whilst walking. She has returned for review at intervals since, and now, twelve months after the operation, her general health and fitness are normal, whilst radiographic examination of the bones (Figure V) shows an almost complete return to normality.

Pathological Investigation of the Tumour.

The smaller of the two specimens removed at operation was merely an involuntary nodule of normal thyreoid. The larger specimen formed a tumour, spheroidal in shape and approximately 1·4 centimetres in diameter. It possessed a thin transparent capsule, whilst the substance of the tumour was fleshy in consistence and in appearance. No areas of degeneration, necrosis, hæmorrhage or cyst formation were visible. Microscopically (Figure V) it was seen to possess an enveloping capsule of fibrous connective tissue, which was sending numerous fine processes or septula into the substance of the tumour. Running in these septula were numerous thin-walled blood vessels,

which in areas became enlarged to form relatively large venous sinusoids, giving the section quite a vascular appearance. Arising from them and passing between the epithelial cells were fine capillary blood vessels.

Supported by this connective tissue framework were cells of parathyreoid type, arranged in sheets or masses. Many of the latter had almost the appearance of acinar spaces; but nowhere in the section were accumulations of "colloid", or acidophile coagulum, seen. The epithelial cells were preponderantly of the principal or chief cell type, and, arranged as they were, they presented quite a striking appearance. They possessed an almost water-clear protoplasm ("*wasserhelle*" cells), due to considerable vesiculation, whilst their nuclei were basal, deep-staining and spheroidal. Surrounding the nuclei were aggregations of eosinophilic granules. Scattered amongst the principal cells were far less numerous eosinophile (oxyphile) cells with dense granular cytoplasm. It is believed that these two varieties of cell represent merely varying degrees of functional activity of the same essential cell type.[30] Most of the cells appeared large and active, although no mitotic figures or giant cells were apparent. Attached to one edge of the section was a small piece of tissue, approximately two millimetres in diameter, which had the histological appearance of normal parathyreoid. No degenerative changes were obvious microscopically.

Discussion.

Although these parathyreoid tumours are usually referred to as "adenomata", there is no evidence of any true autonomous neoplastic process.[30] The presence of large active-looking cells, and even of giant cells, indicates of itself nothing more than functional hyperactivity. The pathological process, therefore, is really a parathyreoid hyperplasia and not a true adenoma. It might be mentioned that malignant tumours of the parathyreoid (carcinomata) are very rare (Jaffe[14]). Biological assay of these tumours for their content of parathormone was performed by Moolten, Clarke and Haywood.[21] In a typical case the parathyreoid tumour which was removed contained 105 units of parathormone per gramme of tumour substance.

As a result of the excessive secretion of parathormone by the parathyreoid tumour changes occur in the bones, consisting of bone removal (resorption), new bone formation and cystic change. Bone resorption occurs partly as a result of halisteresis (removal of calcium due to alteration in the relationship between plasma and bone), partly by lacunar absorption (removal of bone by osteoclasts or foreign body giant cells), and finally by solution about perforating blood vessels. Bone formation occurs by proliferation of cells differentiating as a connective tissue replacing the removed bone and bone marrow. By a process of metaplasia[17] this fibrous connective tissue becomes transformed in varying degree into osteoid tissue—that is, tissue having an appearance like bone but containing little or no calcium.[16] Calcium is scantily deposited, so that eventually, in place of the original hard compact bone of health, we have a structure which is considerably thickened but which consists only of a mass of fibrous and osteoid tissue, with a spongework of bony trabeculæ running through it. Finally, areas of degeneration and hæmorrhage occur, which become surrounded by fibrous connective tissue and foreign body giant cells, resulting in the formation of cysts and giant-celled tumours. There is a close resemblance to these changes in *osteitis deformans* (Paget), but in *osteitis fibrosa* the bone resorption greatly exceeds the new bone formation and the whole process is more extensive and more severe.

Ætiology.

The immediate or proximate cause of *osteitis fibrosa generalisata* has now been established as endocrinal.[13] The osseous lesions are due to excessive secretion of parathormone, occurring as a result of hyperplasia or adenoma of the parathyreoid glands. But what is the ultimate cause of the condition—in other words, what is it that produces the parathyreoid enlargement?

Two hypotheses have been propounded to explain the hyperplastic process affecting the parathyreoid. The first of these theories is that the enlargement is compensatory to a deficiency of vitamin *D*, that deficiency being either direct, due to a lack of dietetic intake of the vitamin, or indirect, due to lack of ultra-violet irradiation. The precise interrelationships of vitamin *D* and parathormone are still uncertain; but it is known that they each play a very important part in calcium metabolism and in regulating the concentration of this mineral in the blood. It is not improbable that the vitamin and the hormone are complementary to each other, so that a deficiency of one of them, for example the vitamin, necessitates a reciprocal increase in the other; hence a compensatory hyperplasia of the parathyreoids occurs. Goodale[35] and Higgins and Sheard[11] have shown that deprivation of ultra-violet light in chicks deprived of other sources of vitamin *D* results in hyperplasia and enlargement of the parathyreoid glands. Also Wilder, Higgins and Sheard[34] have shown that this hyperplasia can be prevented to some extent by the injection of parathyreoid extract. A similar parathyreoid enlargement, believed to be compensatory, may occur in other decalcifying and avitaminotic affections of the skeleton, for example in osteomalacia. If, however, the parathyreoid enlargement in *osteitis fibrosa* is compensatory and is occurring as a result of lack of vitamin *D*, why does hypercalcæmia occur and why does the removal of the tumour relieve the condition? The explanation offered is the following. In vitamin *D* deficiency compensatory enlargement of the parathyreoid is believed to occur (as proven in the case of chicks). In most cases the hyperplasia is not overdone and the increased supply of parathormone produced does not exceed the increased demand for it. Occasionally, however, overcompensation occurs, giving rise to increased secretion of parathormone and resulting in hyperparathyreoidism and *osteitis fibrosa cystica*. This is analogous to the response of the thyreoid gland to iodine deficiency, and the adenoma in either case may or may not become toxic. Whether generalized parathyreoid hyperplasia or a solitary "adenoma" occurs depends on the responsiveness of all or one of the glands. Evidence in favour of the above theory, as applicable to man, is believed to lie in the geographical distribution of the disease, which

is commonest in countries deficient in ultra-violet light and vitamin *D*, and rare in sunny countries like Australia.[33] Also many of these patients have a dislike for milk and other foods rich in vitamin *D* and calcium (D. Hunter).

The second hypothesis is based upon the function which the pituitary gland is now believed to perform in the control and regulation of the activities of the other ductless glands. It has long been realized that subtotal thyreoidectomy, whilst it relieved the symptoms of thyreotoxicosis, did not cure the condition. Moreover, not only did exophthalmos usually persist, but recurrence of the disease was not infrequent. It is now believed by many that the primary disturbance in thyreotoxicosis is pituitary, as a result of which hypersecretion of the thyreotropic hormone occurs. It is this persistent pituitary hormonal hypersecretion (unaffected by thyreoidectomy) which is the cause of the persistence of exophthalmos and the continued state of metabolic abnormality. A similar pituitary hormone is believed to control the parathyreoid apparatus and it is not improbable that a similar pituitary disturbance, resulting in excessive secretion of the parathyreotropic hormone, is the ultimate cause of hyperparathyreoidism. In support of this conception is the frequent persistence of abnormal metabolism after parathyreoidectomy. Thus not infrequently the hypercalcæmia and hypercalcuria persist, increase in density of the bones fails to occur, and there may be a return of symptoms even after an apparently successful parathyreoidectomy.[12] Some cases are also associated with definite evidence of endocrinal dyscrasia, for example the five cases reported by Albright, Butler, Hampton and Smith;[1] in these generalized *osteitis fibrosa* was associated with cutaneous pigmentation, endocrine dysfunction and precocious puberty. Frank and Hjerrild[7] have also reported a case of parathyreoid adenoma associated with a diffuse hyperplasia of the basophile elements of the anterior lobe of the pituitary. Such findings may be purely fortuitous, but nevertheless lend some support to a possible ultimate endocrinal origin in the pituitary.

Predisposing Conditions.

The age of the patient is of little help in diagnosis, as *osteitis fibrosa* has been found occurring at all periods of life. Statistically it occurs most frequently between the ages of thirty and fifty years. Nevertheless the condition has been diagnosed and treated in patients from the age of thirteen years to as much as seventy-four years. Recently Landon[19] has reported successful diagnosis and treatment of the condition in a child aged two and a half years.

Females are affected much more frequently than are males, the incidence among the former being three times greater than among the latter. No familial incidence has ever been suggested, although its occurrence in siblings (a brother and a sister) has been recorded.[8]

The geographical incidence of the reports of proven cases has been worked out by Wilder and Howell.[31] A modification of their results is as follows:

North American continent	41%
Great Britain	16%
Germany and Austria	16%
Scandinavia and Netherlands	14%
France	8%
Italy	4%
Australia	1%
	100%

Symptomatology and Diagnosis.

The clinical features of generalized *osteitis fibrosa* may be summarized. It is a disease of slow onset and progressive course, characterized by bone pains, bone deformity and spontaneous fracture. Indeed it is the latter, resulting in an X ray examination of the skeleton, which gives the lead to diagnosis in the majority of cases. Difficulty arises, however, owing to the fact that such a syndrome may occur in a number of different pathological conditions. They are, in order of incidence, the following: (i) carcinomatosis of bone occurring secondary to some primary tumour, which may or may not be evident; (ii) multiple myelomatosis; (iii) *osteitis fibrosa cystica generalisata*. Clinically these conditions may be indistinguishable. One feature which may be of value in differential diagnosis is the actual duration of symptoms; for example, if the symptoms have been present for more than twelve months and no primary neoplasm has been discovered, the lesion is unlikely to be carcinomatosis.

Various special investigations are performed to confirm or establish the precise diagnosis. They are the following: (i) X ray examination of the skeleton; (ii) biochemical investigation of the serum calcium, serum phosphate and plasma phosphatase contents, and of the calcium balance; (iii) examination of the urine for Bence-Jones protein.

The discovery of Bence-Jones proteins in the urine almost invariably indicates disease of the bone marrow and is very suggestive of multiple myelomatosis. Occasionally, however, these proteins are found in association with secondary malignant disease of bone.[35]

Estimations of the serum calcium and serum phosphate contents are of first-rate importance in suspected cases. In a patient with the appropriate clinical findings a rise in the serum calcium level, for example to 12 or up to 20 milligrammes *per centum*, associated with a reciprocal fall in the serum phosphate content, for example to 0·3 or up to 3·0 milligrammes *per centum*, is almost diagnostic. The calcium and phosphate values, to be of significance, must vary reciprocally (as above), for a high serum calcium content with no change in the serum phosphate content is not infrequently found in multiple carcinomatosis of bone. Multiple myelomatosis may give a biochemical picture similar to that of *osteitis fibrosa*. The plasma phosphatase level is raised in *osteitis fibrosa*; in this case it was raised as much as six to ten units. Similar rises, however, occur in *osteitis deformans*, secondary osseous carcinomatosis, rickets and renal rickets,

and osteogenic sarcoma. The plasma phosphatase content forms an index of osteoblastic or osteoclastic activity. In focal *osteitis fibrosa* the phosphatase value is normal.

The calcium balance is determined in cases which are still obscure, for example when the serum calcium content is normal or nearly normal through active renal excretion. Patients with *osteitis fibrosa* have a negative calcium balance—that is, their calcium excretion is greater than their calcium intake. Determination of the serum calcium content alone is likened by Hunter to the estimation of the height of a river. It gives no information as to the direction in which flow is occurring, whether to or from the bones. The calcium balance presents this information.

X ray examination is probably of greatest importance, and in the later stages of the disease, when generalized bone cysts are present, is practically diagnostic. Such findings occur specially in the large bones and the scapula, and are associated with generalized decalcification and osteoporosis. In the really early stages of the disease, however, the radiographic picture may be far from typical, as in the case cited here, in which the resemblance to a single and later multiple carcinomatosis of bone was very close. Only months afterwards was the true nature of the condition apparent. The radiographs of this case are therefore of particular interest, showing as they do the progression of changes as they occurred over a period of nearly three years. These changes include the gradual alteration in appearance from a condition so closely simulating carcinomatosis that such a diagnosis was almost inevitable, up to those of the present time, when the true nature of the condition is obvious and a definite diagnosis can be made.

Summary.

1. A case of generalized *osteitis fibrosa cystica* with parathyreoid tumour is reported.

2. The difficulties experienced in diagnosis are discussed and an account of successful treatment is given.

3. The literature on the subject is reviewed.

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References.

(1) F. Albright, A. M. Butler, A. O. Hampton and P. Smith: "Syndrome Characterized by Osteitis Fibrosa Disseminata, Areas of Pigmentation and Endocrine Dysfunction, with Precocious Puberty in Females; Report of Five Cases", *The New England Journal of Medicine*, Volume CCXVI, April 29, 1937, page 727.

(2) E. N. Allott and J. Jemson: "Generalised Osteitis Fibrosa due to Retro-Œsophageal Parathyroid Tumour", *The Lancet*, Volume I, March 12, 1938, page 609.

(3) E. D. Churchill and O. Cope: "Parathyroid Tumours Associated with Hyperparathyroidism; Eleven Cases Treated by Operation", *Surgery, Gynecology and Obstetrics*, Volume LVIII, February, 1934, page 255.

(4) J. B. Collip: "The Parathyroid Glands", *Medicine*, Volume V, 1926, page 1.

(5) J. W. Dawson and J. W. Struthers: "Generalized Osteitis Fibrosa with Parathyroid Tumour and Metastatic Calcification, including a Critical Discussion of the Pathological Processes Underlying Osseous Dystrophies", *Edinburgh Medical Journal*, Volume XXX, 1923, page 421.

(6) J. Erdheim: *Mittheilungen aus den Grenzgebieten der Medicin und Chirurgie*, Volume XVI, 1906, page 632.

(7) S. Franck and N. Hjerrild: "Case of Recurrent Generalized Osteitis Fibrosa (Recklinghausen) with Parathyroid Adenoma and Diffuse Hyperplasia of Basophil Elements in Anterior Lobe of Pituitary", *Hospitalstidende*, Volume LXXX, October 12, 1937, page 1117.

(8) L. Goldman and F. Smyth: "Hyperparathyroidism in Siblings", *Annals of Surgery*, Volume CIV, December, 1936, page 971.

(9) A. B. Gutman, P. C. Swenson and W. B. Parsons: "The Differential Diagnosis of Hyperparathyroidism", *The Journal of the American Medical Association*, Volume CIII, July, 1934, page 87.

(10) R. R. Hannon, E. Shorr, W. S. McClellan and E. F. Du Bois: "Case of Osteitis Fibrosa Cystica (Osteomalacia?) with Evidence of Hyperactivity of Parathyroid Bodies: Metabolic Study", *The Journal of Clinical Investigation*, Volume VIII, 1930, page 215.

(11) G. M. Higgins and C. Sheard: "Effects of Selective Solar Irradiation on Parathyreoid Glands of Chicks", *The American Journal of Physiology*, Volume LXXXV, June, 1928, pages 290 and 299.

(12) Hoffheinz: *"Ueber Vergrösserungen der Epithelkörperchen bei Ostitis fibrosa und verwandten Krankheitsbildern"*, *Virchows Archiv*, Volume CCLVI, 1925, page 705.

(13) D. Hunter: "Hyperparathyroidism: Generalized Osteitis Fibrosa", *The British Journal of Surgery*, Volume XIX, 1931-1932, page 203.

(14) H. L. Jaffe: "Hyperparathyroidism (Recklinghausen's Disease of Bone)", *Archives of Pathology*, Volume XVI, 1933, page 63.

(15) Kaye-Scott: *Royal Melbourne Hospital Clinical Reports*, Volume IV, 1933, page 105.

(16) S. J. King: "Localized Rarefying Conditions of Bone", 1935, page 69.

(17) R. L. Knaggs: "Inflammatory and Toxic Diseases of Bone", 1926, page 257.

(18) F. H. Lahey and G. E. Haggart: "Hyperparathyroidism: Clinical Diagnosis and Operative Technique of Parathyroidectomy", *Surgery, Gynecology and Obstetrics*, Volume LX, June, 1935, page 1033.

(19) J. F. Landon: "Parathyroidectomy in Generalized Osteitis Fibrosa Cystica: Report of a Case in a Child Two and a Half Years of Age", *The Journal of Pediatrics*, Volume I, November, 1932, page 544.

(20) F. Mandl: *"Therapeutischer Versuch bei einem Falle von Ostitis fibrosa generalisata mittels Exstirpation eines Epithelkörperchentumors"*, *Zentralblatt für Chirurgie*, Volume LIII, 1926, page 260.

(21) S. E. Mooltea, F. M. Clarke and H. Haywood: "Bio-Assay of a Parathyroid Adenoma in a Case of Generalized Osteitis Fibrosa", *The Journal of the American Medical Association*, Volume CVIII, 1937, page 111.

(22) J. J. Morton: "The Generalized Type of Osteitis Fibrosa Cystica, von Recklinghausen's Disease", *Archives of Surgery*, Volume IV, 1922, page 534.

(23) J. F. Nonidez and H. D. Goodale: "Histological Studies on Endocrines of Chicks Deprived of Ultraviolet Light; Parathyroids", *The American Journal of Anatomy*, Volume XXXVIII, January, 1927, page 319.

(24) J. Paget: *Medico-Chirurgical Transactions*, Volume LXV, 1882, page 225.

(25) F. von Recklinghausen: *"Die fibrose oder deformirende Ostitis"*, *Festschrift Virchow*, 1891.

(26) E. P. Richardson, J. C. Aub and W. Bauer: "Parathyroidectomy in Osteomalacia", *Annals of Surgery*, Volume XC, October, 1929, page 730.

(27) K. Ross: "Generalized Osteitis Fibrosa with Parathyroid Adenoma", *The Australian and New Zealand Journal of Surgery*, Volume IV, 1935, page 407.

(28) Schlangenhaufer: *"Zwei Fälle von Parathyreoidtumoren"*, *Wiener Klinische Wochenschrift*, Volume XXVIII, 1915, page 1362.

(29) I. Snapper: "Parathyroid Tumour and Changes of Bone", *Archives of Internal Medicine*, Volume XLVI, September, 1930, page 502.

(30) H. M. Turnbull: "Observations upon the Bones, the Parathyroid Tumours and Normal Parathyroid Glands", *The British Journal of Surgery*, Volume XIX, 1931-1932, pages 222 and 223.

(31) A. J. Walton: "Surgical Treatment of Parathyroid Tumours", *The British Journal of Surgery*, Volume XIX, October, 1931, page 285.

(32) Weil, cited by J. A. Lièvre: *"L'Ostéose Parathyroïdienne et les Ostéopathies Chroniques"*, 1932, page 18.

(33) R. M. Wilder and L. P. Howell: "Ætiology and Diagnosis in Hyperparathyroidism: Review of 135 Proved Cases", *The Journal of the American Medical Association*, Volume CVI, February 8, 1936, page 427.

(34) R. M. Wilder, G. M. Higgins and C. Sheard: "Significance of Hypertrophy and Hyperplasia of Parathyroid Glands in Rickets and Osteomalacia", *Annals of Internal Medicine*, Volume VII, March, 1934, page 1059.

(35) R. A. Willis: "The Spread of Tumours in the Human Body", 1934, page 344.

Reviews.

PROBLEMS OF INCREASING AGE.

How many doctors know anything about the medical problems of increasing age? Very few; our teachers say little about it, and we see but a scanty number of patients in ward or out-patient department whose only complaint is old age. But as old age is a daily problem, we must fumble along, no doubt doing our best, but working more by guess than by knowledge. Not only are we ignorant, but from the present trend of life problems of old age are in future likely to be much more common than the problems of childhood and infancy. The average expectation of life is increasing steadily, and the proportion of young people is growing less. Thus in the United States at the beginning of the nineteenth century this expectation was 35·5 years; by 1850 it had risen to forty; but by 1900 it had jumped to 50; by 1920 to 55; and by 1930 had risen to a little over 60 years. Even now the process has not ceased and regularly the "Statistical Bulletins" of the Metropolitan Life Assurance Society of New York call attention to the decline in mortality and the increase in length of life.

A book dealing comprehensively with old age and its problems should therefore meet a very real demand, and such a book is that published by the Josiah Macy Junior Foundation.[1] It is edited by E. V. Cowdry of Washington University, St. Louis, and includes contributions from a host of distinguished writers, who cover all aspects of the problem. Thus Lewellys F. Barker, Emeritus Professor of Medicine at Johns Hopkins University, writes on "Ageing from the Point of View of the Clinician". "Ageing of the Nervous System", by Macdonald Critchley of London, "The Eye", by Jonas S. Friedenwald, "The Female Reproductive System", by Edgar Allen, are only a few that spring to the eye. In fact, it was not found possible to think of any aspect of old age which had not been discussed and well discussed in a learned and lucid article; for example, W. B. Cannon's short essay on "Homeostatic Mechanisms" is a model of scientific writing, dealing as it does with those difficult problems of chemical regulation which play so important a part in our life history.

Among such a mass of good material it is difficult to pick out the most interesting; the choice would depend so much on the particular interests of the reader. Thus to an insurance physician Louis J. Dublin's article on "Longevity", with its study of longevity in the mass and the individual, will be of absorbing interest, while the orthopædic surgeon will find much in Professor T. Wingate Todd's article on "The Skeleton and Locomotor System", where a biochemist would turn to C. N. McCay's paper on "Chemical Aspects". To complete the range of the investigation there are articles by accepted authorities dealing with the ageing of plants, protozoa, and insects.

We have found three chapters of outstanding interest and merit. The first is the "Introduction", by John Dewey, an exposition of the philosophy of old age that might well be printed as a separate monograph. Inevitably he quotes Browning, but most curiously he omits Cicero, whose "*De Senectute*" must be familiar to many students. Next Barker's article, "Ageing from the Point of View of the Clinician", is remarkable for its breadth of clinical knowledge and its lucid exposition, but most for the charming humanism that runs through it. Like that of his predecessor, Osler, the author's general reading is wide; he quotes the Greek mythology, Swift, the Ninetieth Psalm, and Cicero. His knowledge of medicine is as wide as his reading.

Macdonald Critchley's essay on the "Nervous System" is of a different type. It is strictly objective—it deals with solid clinical facts, marshalled and classified with a "summary" to drive them home. Yet, when read, it leaves a feeling of remarkable completeness and clarity.

But it would be easy to go on picking and choosing—the mass of information is so vast. What, for instance, is the longest lived insect? And why is coronary disease more common in the *ramus descendens anterior* of the coronary arteries? These are only two samples taken at random of the innumerable pieces of information contained in the book. It is hardly to be read at a single sitting; it is too solid a meal for that, but it is one for browsing as well as for reference. Add to this the fact that the printing is excellent, the binding good and flexible (without being attractive to the ever-ready cockroach), and the whole is a model volume. It is one of those rare books of which it is possible to write: "It should be a book of reference for every serious physician."

[1] "Problems of Ageing: Biological and Medical Aspects", edited by E. V. Cowdry; a publication of The Josiah Macy Junior Foundation; 1939. London: Baillière, Tindall and Cox. Medium 8vo, pp. 788, with illustrations. Price: 45s. net.

PROGRESS IN HÆMATOLOGY.

In producing the fourth edition of "Recent Advances in Hæmatology" Dr. A. Piney has followed his earlier procedure and given in a convenient, concise and clear manner a statement of the present position of hæmatology.[1] This necessarily includes the recent advances in knowledge, and the changes in this branch of medicine during the last decade have been so great and so diverse that the author has found it necessary to rewrite almost all of the material.

Commencing with a discussion of the origin and development of blood cells and a description of the various formed elements in the blood and bone marrow, he passes on to describe and discuss symptomatic blood changes, various types of anæmia, the leuchæmias, erythræmia, hæmorrhagic diseases, glandular fever, and diseases affecting the reticulo-endothelial system. Concise descriptions of the ætiology, the symptomatology and the changes in the hæmopoietic system are given, and illustrative short case reports are freely interspersed throughout. The appropriate treatment for each clinical entity is described briefly. A useful glossary is appended; and in addition to a bibliography which details the more important works of reference, at the end of each chapter there are valuable lists of references.

Piney still stresses his views regarding the lack of relationship between megaloblasts and normoblasts, but states quite fairly the views of those who maintain that these cells are not fundamentally different. There seems to be nothing gained by maintaining that there is a fundamental difference, and the weight of evidence is certainly in favour of the contention that the so-called megaloblast is a primary erythroblast with an abnormal shift of ripening of the cytoplasm to the left. The only possible advantage to be gained from retention of the term is that it indicates, as a result of popular usage, the abnormal large nucleated cell of the erythrocyte series which is found in anæmia of the pernicious type. The space taken to discuss this aspect of the blood in pernicious anæmia might be used to greater advantage in giving a more detailed account of the initial treatment of patients suffering from the disease.

In such an excellent publication it is disconcerting to find that it is stated on page 34 that in normal bone marrow "the fatty change spreads proximally more rapidly than distally", and that the figures on pages 47 to 48 are wrongly numbered and bear no evident relation to the text. On page 177 appears the statement that "cases ended fatally rather than quickly; . . . eight weeks after the onset of symptoms". A few spelling errors were noticed, namely, "Huntington" on page 235, and "disfunction" on page 247.

"Recent Advances in Hæmatology" is well written, contains numerous excellent illustrations and comprehensive references, and can be recommended to both graduates and undergraduates who wish to bring their knowledge of the subject up to date.

[1] "Recent Advances in Hæmatology", by A. Piney, M.D., Ch.B., M.R.C.P.; Fourth Edition; 1939. London: J. and A. Churchill Limited. Large crown 8vo, pp. 310, with 8 coloured plates and 34 text figures. Price: 15s. net.

The Medical Journal of Australia

SATURDAY, DECEMBER 2, 1939.

All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given without abbreviation: Initials of author, surname of author, full title of article, name of journal, volume, full date (month, day and year), number of the first page of the article. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

THE CONTROL OF RHEUMATIC FEVER.

In a recent issue reference was made in these pages to the treatment of children affected by rheumatism and to the shortage of beds for rheumatic children in metropolitan children's hospitals; prevention, which is a natural corollary to such a discussion, was merely mentioned. For the sake of completeness, if for no other reason, prevention should be discussed; but an added reason is a recent discussion by J. A. Glover[1] on rheumatic fever in the "Control of the Common Fever" series appearing in *The Lancet*. Moreover, interest in rheumatism has been manifest during recent months in many parts of the Commonwealth, chiefly because it was selected as the principal subject for consideration at the Perth session of congress. The postponement of the congress must not be made an excuse for neglect of the study of this important disease.

Any consideration of the prevention of acute rheumatism must of necessity mean a recapitulation of previous discussions. The first and most important fact to be remembered is that the cause of rheumatic infection has not yet been determined. Since Poynton and Paine first stated their conviction in 1900 that a streptococcus was responsible, many investigators have reported work that supports this view. At the same time the contention that rheumatism is a virus disease cannot be lightly dismissed. This view was discussed in these pages in the issue of November 13, 1937, at page 885. That a streptococcus is an essential factor appears certain; but if a virus is concerned the streptococcus must be given a secondary place. In the present state of knowledge most workers will agree with Glover that for practical purposes measures of control should be based on the view that acute rheumatism is the result of streptococcal infection. He points out that this attitude is supported epidemiologically by resemblances, observed for over eighty years, between the trend and oscillations of the mortality rates of rheumatic fever and those of such streptococcal diseases as scarlet fever, erysipelas, septicæmia and puerperal fever.

In any attempt to control an infective process attention must be paid to the infecting agent and the state of the person affected—to the seed and the soil. In other words, we must not only know the conditions which favour the growth, the virulence and the spread of the organism, but we must study those that lower the resistance of the person attacked. Glover, in discussing these factors, refers on the one hand to overcrowding, defective ventilation and the presence of catarrhal diseases, such as influenza and measles, which increase the spraying capacity of the carrier, and on the other hand to "rheumatic heredity", insufficient food, the lack of protective foods, dampness of house or site, fatigue, antecedent disease, and (a point often overlooked) recent arrival in a large community. Obviously a chapter could be written on each of these factors, and around some of them, such as a "rheumatic heredity", much controversy might take place. Glover states that on consideration of these factors the prevention of rheumatic fever is best presented from three aspects: (*a*) epidemics in semi-closed communities, (*b*) sporadic cases occurring in children or young adults living at home, (*c*) recurrences in rheumatic wards or hospital schools of recovery. He holds that in rheumatic fever more is to be learned from an epidemic of a dozen cases

[1] *The Lancet*, February 25, 1939.

than from a hundred apparently sporadic cases. The sequence in epidemics in semi-closed communities is usually as follows:

1. Overcrowding, usually with a rapid flow of newcomers.
2. The rise of the carrier-rate of *S. pyogenes* to a high percentage (40-50 per cent.) and the concomitant great predominance of one serological type, the so-called "epidemic strain"; this constitutes the "carrier epidemic".
3. The tonsillitis (or "case") epidemic.
4. The occurrence of cases of rheumatic fever. These at worst seldom number a tenth of the cases of tonsillitis.

In order to control outbreaks of this kind it is necessary to reduce the carrier rate by "spacing out", by improved ventilation and by the prompt isolation of patients with tonsillitis. In his remarks on sporadic cases of acute rheumatism occurring in children Glover makes statements which should be broadcast far and wide. He insists that the responsibility for the prevention of sporadic cases is shared by the medical practitioner, the public health authority and the education authority. Among the duties of the State are the provision of proper, uncrowded and damp-free housing, the relief of poverty and the provision of supplementary feeding for necessitous subnormal children. Schools should provide facilities for the drying of outdoor clothing and for the changing of wet shoes—more needed in England than in the Australian climate. The heating and ventilation of schools are also important. Here we would state that we have nothing but approval for the efforts of one section of the Australian Press to shame educational authorities to undertake the heating of schools in the winter months. Glover's statements about the responsibilities of the medical practitioner in diagnosis and treatment need not be set out. Emphasis may perhaps be placed, however, on the need for supervision of children who have recently recovered from a rheumatic infection. This again raises the question of convalescent homes for children, mentioned in our previous discussion.

From this short survey it is quite clear that much can be done to prevent rheumatic infection in Australia if the information already obtained is supplemented and efforts are made to apply available knowledge. A special group has been formed in the British Medical Association in Australia for the study of rheumatism and the discovery of new facts. Even though the nation is at war this study can be made. An organized effort, begun in a small way, will soon grow; the fascination of the subject alone would ensure this growth. The cares and anxieties of the present should not be allowed to prejudice the welfare of future generations.

Current Comment.

THE SURGICAL TREATMENT OF PATENT DUCTUS ARTERIOSUS.

In May of this year, in his discussion on the surgical management of the patent *ductus arteriosus* before the American Surgical Association,[1] Robert E. Gross presented accounts of four successful cases. As long ago as 1907 J. C. Munro suggested that the patent vessel should be tied, and several surgeons since then have made the attempt without success.

It appears that the essential preliminary steps are to confirm the diagnosis and then to decide whether operative interference is justifiable. Several years may elapse before the clinician can find anything more definite than "congenital heart disease". During the first twelve months of life even the murmur, thrill or cardiac enlargement may be absent. By the fourth or fifth year the fully developed picture may be present, having as its outstanding features a continuous murmur with systolic accentuation, precordial thrill, sharp second pulmonary sound, cardiac enlargement and a low diastolic blood pressure. Two other features are found by X ray examination—increased pulmonary markings due to congestion in the pulmonary circulation, and prominence of the pulmonary arterial shadow. It is hardly likely that the first of these is of great diagnostic value, and the second finding does not appear to be very marked in the photographs accompanying the article. A normal electrocardiogram is stated to be usual in the absence of any other pathological condition.

The cases suitable for surgical treatment are not easy to determine. Aortic and pulmonary stenosis are possible factors in the causation of the patent ductus. Closure of the shunt in these cases will throw too big a strain on the heart. A septal opening and a mild degree of initial stenosis are said not to be contraindications. It must be remembered that once the first year of life is past some patients with this congenital defect go through life with little disability. In the Cincinnati General Hospital 489 autopsies were performed on patients with this condition. Of these, 231 were stillborn, 176 died during the first week, and all except one died within eight months of birth. Statistics regarding the prognosis in those who survive this first year are difficult to obtain, since

[1] *Annals of Surgery*, September, 1939.

those who died or who need medical attention are reported and those who died of natural causes late in life are not. Maude Abbott collected 92 uncomplicated cases, and it would seem from her figures that 25% of patients died of bacterial endocarditis and half died from cardiac failure. The average age at death was twenty-four years. The prognosis was mentioned in our issue of November 11, 1939, in an abstract of a paper by Gross, Emerson and Green that appeared in the August, 1939, issue of *Surgery*. A surgeon would hesitate, therefore, before operating upon a patient whose cardio-vascular efficiency was sufficient for normal existence. The suitable type of case suggested is one in which there is no evidence that the patency of the duct is being cured naturally, when the individual is not developing properly or when the heart is carrying an increased burden. Bacterial endocarditis is looked upon as a contraindication for fear that a fatal bacteriæmia may be caused.

In the discussion of the technical difficulties Gross points out the dangers from the anatomical point of view and how to avoid them. It is certain that the pleural cavity (on the left side) will remain widely open for at least one hour during the operation, which is performed under cyclopropane anæsthesia. Despite this the patients are said to be remarkably free from shock and post-operative reaction. Gross allowed his patients out of bed in a few days, in one case in twenty-four hours; and they were discharged from hospital in about two weeks' time. This is a remarkable result among patients with minor degrees of cardiac insufficiency, operated on in childhood. The subsequent improvement was rapid.

When Maude Abbott's statistics are examined in the light of these results it would appear that more patients are suitable for operation than is suggested. When a case is diagnosed in childhood after the age of four years it seems that the patient has only one chance in four of living a healthy life, and that the average expectation of life is only twenty-four years. Time alone will tell whether the operation is as safe as has been the experience of Gross. If so, a definite advance has been made in cardio-vascular surgery.

BLOOD PRESERVATION.

MUCH has been written lately on the use of stored blood for intravenous transfusion. In England, Russia and North America, "blood banks" have been established in many hospitals. There is, however, a growing conviction that blood kept too long is dangerous, as evidenced by an occasional severe reaction, a greater incidence of post-transfusion jaundice and an occasional unexplained death. John Scudder, Charles R. Drew, Dorothy R. Corcoran and David C. Bull[1] have investigated one of the abnormalities of stored blood, namely, the loss of potassium from the cells and its increase in the plasma. With regard to the importance of this loss, they state that the manifestations of potassium poisoning have been well known since 1840 and observe that such poisoning is not peculiar to the animal kingdom, since alterations in the concentration of potassium in certain plant cells or in the media in which they live have a profound effect on the life and growth of plants. From a study of the literature and from their own independent observations, these writers draw the following conclusions about the toxicity of potassium.

1. The parenteral administration of potassium is associated with toxic manifestations of both muscular and nervous tissue together with a depression of the central nervous system.
2. The almost specific action of potassium is exerted on the heart and circulation, with disturbances varying from diminished cardiac output to immediate diastolic arrest.
3. The lethal doses previously reported for animals have been confirmed.
4. The rate of injection is of great importance, for when potassium is given slowly, several times the usual lethal dose is tolerated.
5. Recovery may be effected by artificial respiration, cardiac massage, the use of oxygen, injections of salt solution, and administration of cortical extract in large doses.

These conclusions are, of course, based largely on animal experiments. As to the possibility of the occurrence of potassium poisoning following the transfusion of stored blood, Scudder and his associates have shown that there is a daily increase in the plasma potassium of preserved blood kept under aseptic, bacteriostatic conditions, with increments reaching as high as 1,000%. Of the many preservatives tested, none prevented the diffusion of potassium from the cells. In several instances hæmolysis was slow and in one it did not take place at all, yet the diffusion of potassium was not altered. In the remainder hæmolysis occurred; in some it started as early as the fifth day. All this illustrates the inadequacy of present methods of storage. Agitation, such as shaking, appears to hasten the loss of potassium from the cells. Moreover, the shape of the container influences the rate of potassium diffusion; the greater the interface area between the cells and the supernatant plasma, the greater the rate of diffusion. This suggests that tubular containers may be preferable to wide-bottomed flasks.

The intravenous lethal dose of potassium in man is not known. Studies on animals suggest that a rapid transfusion of from three to five litres of blood with a plasma content of 100 milligrammes per 100 cubic centimetres would be necessary to kill an adult. Blood preserved for thirty days would contain potassium at this level. Blood preserved for more than five days by the methods now in use might contain sufficient potassium to cause toxic manifestations. To the action of potassium in the plasma of stored blood there might, of course, be added the effect of potassium liberated by minor degrees of hæmolysis occurring during transfusion.

The writers make no claim that the increase of potassium in plasma is the only danger in the giving of stored blood. Many other disadvantages have already been described by other workers.

[1] *The Journal of the American Medical Association*, June 3, 1939.

Abstracts from Current Medical Literature.

OPHTHALMOLOGY.

Unilateral Hydrophthalmia and its Inheritance.

CUSTODIS (*Klinische Monatsblätter für Augenheilkunde*, February, 1939) has reported a genealogy revealing unilateral hydrophthalmia. The patient, his older brother and his only son were affected. No other ocular defects were found in any members of the family, and the other eyes of the affected members were normal. It is rarely that an opportunity for the study of heredity in this disease occurs. The bilateral form is usually recessive. The author prefers to assume that the inheritance is of a digenic dominant type, in which the lesion becomes manifest only through a combination of two hereditary factors. He does not think that the inheritance is recessive and sex linked. Under German regulations patients with unilateral hydrophthalmia need not be sterilized; they, however, are registered, and the minister of health would prevent them from marrying into families with any other deformities, particularly if ocular. It has not yet been proved that descendants of hereditary unilateral hydrophthalmia cannot develop the bilateral form of the disease. The author points out that by sterilization a great many valuable hereditary natural tendencies perish with the deformity or inherited disease. He concludes that it is against the best interests of the population as a whole that there should be an unrestricted reduction of quantity in favour of quality.

Vitamin A Therapy in Corneal Diseases.

S. K. KENTGENS (*Ophthalmologica*, Volume XXVI, 1938, page 3) has determined the vitamin *A* content of the blood in corneal diseases and has studied the results of general and local vitamin *A* therapy. He investigated 17 patients with corneal herpes and found that though the vitamin *A* content of the blood of a series of average patients coming purely for a test of refraction, whom he used as controls, was low, yet that of these affected patients was so much lower that he considered this disease a hypovitaminosis *A*. The results of treatment of 26 patients by vitamin therapy were more rapid than those of 19 patients with herpes not treated in this way. The total times taken were 249 and 584 days, and the average duration was 10 days and 30 days. Similar benefits were derived by nine patients suffering from non-herpetic superficial punctate keratitis. The author treated five patients suffering from marginal ulceration and no improvement beyond that following the usual treatment was observed. Though the condition of catarrhal ulceration is similar, yet vitamin therapy favourably influenced the condition of these patients. His conclusions regarding the benefit derived by patients suffering from scrofulous keratoconjunctivitis were indefinite. He formed a general impression that their condition was improved. His results in two cases of Mooren's ulceration were good, confirming those of Judkin, Orten and Smith. Two patients suffering from Groenouw's type of epithelial degeneration were treated without benefit. On the other hand, an unusual degeneration healed completely in six weeks. The author considers that two infants suffering from *ophthalmia neonatorum* with corneal ulceration obtained much better results than they would have obtained without vitamin *A* therapy.

Post-Operative Detachment of Choroid after Total Extraction of Cataract.

P. BONNET AND E. GRANDDEMENT (*Archives d'Ophthalmologie*, January, 1939) report six cases of dome-like chorioidal detachment following total extraction of cataract with Arruga's capsule forceps. The article is illustrated by beautiful colour pictures. The detachment was observed first on the nasal side and extended in a day or two to the temporal side. In two cases it was accompanied or preceded by a shallow detachment of the retina, and this latter persisted for a day or two after subsidence of the chorioidal detachment. Accepting generally the classical teaching of the Fuchs school that post-operative detachment of the choroid usually subsides in two or three weeks and leaves no impairment of vision in its train, the authors point to cases reported as lasting several months, and to instances of marked reduction of vision accompanying the detachment and persisting after the choroid had been reapplied. In one of their cases vision was lowered from $^{5}/_{10}$ to $^{2}/_{10}$ even at the end of eight months. Traces of the disturbance may be seen in the form of partial atrophy of the choroid or extensive formation of scar tissue in the affected areas. The diagnosis is made by the discovery of smooth dome-like prominences projecting into the pupillary area from one or both sides, usually of a sombre grey colour, sometimes marked by a deep groove caused by the pressure of one of the vortex veins, which limit the extension backwards of the detachment. This colour may be darker and acquire a slight reddish tint if the subchorioidal fluid is blood-stained and not serous, as usually is the case. For the differential diagnosis from serous effusion and hæmorrhage and, above all, from tumour, examination by transillumination is invaluable. Transillumination also reveals the precise limits of the detachment and the pigmentation, which in many cases occurs at the limit. The authors agree with Fuchs in attributing the detachment to transudation from the choroid created at the moment when the intraocular pressure is suddenly lowered, either by section or by the trephining of the sclera-cornea. The authors do not regard the occurrence of this accident as a result of any fault in operative technique, but are disposed to lay stress on the role of advanced age, with its accompaniment of rigid sclera, on increased intraocular tension, notably in operations undertaken for glaucoma, on the congested state of the chorioidal vessels, often seen in diabetics (two of their patients had signs of glycosuria), and on the vascular disturbances associated with chronic renal disease.

Treatment of Diseases of the Eye with Grenz Rays.

R. L. PFEIFFER (*Archives of Ophthalmology*, June, 1939) describes the use and effects of *Grenz* rays upon surface lesions of the eyeball, cornea, bulbar conjunctiva, episclera and sclera. *Grenz* rays have a wave length between that of ultra-violet and that of Röntgen rays; they are generated in a hot cathode vacuum tube, as are Röntgen rays, but at a much lower voltage. Their use is most successful in corneal ulcers, episcleritis and scleritis. They are safe and analgesic and may well replace other forms of radiant energy in their field of usefulness.

Ocular Complications of von Recklinghausen's Neurofibromatosis.

W. MEYER (*Klinische Monatsblätter für Augenheilkunde*, July, 1939) gives a résumé of the ocular complications of von Recklinghausen's neurofibromatosis. In addition to neuromata of the upper lids, exophthalmos from retrobulbar extension, congenital hydrophthalmos, megalophthalmos, and excessive pigmentation of the macula may be found. Rarely also plexiform neurofibromata may involve the lids, or unilateral hypertrophy of the face due to involvement of the first branch of the trigeminal nerve may be present. In the lids the disease extends from the perineurium to include the connective tissue, and thereby produces an elephantiasis. Hence the name *elephantiasis neuromatodes* which is commonly given to it. Incomplete examination accounts for those cases in which evidence of neurofibromatosis elsewhere in the body is not found. The lesions may be situated in the deeper layers of the skin and escape observation. A patient, twenty-nine years of age, seen by the author, presented a tumour of the upper lid, which was overhanging the lower lid. The tumour was divided into two unequal portions by a sulcus seen on the conjunctival aspect. Five years previously a dermatologist had found papulonecrotic tuberculide lesions on the skin of his back, which were quiescent at the time the ocular tumour was examined. Histological examination of the tumour revealed an inflammatory reaction in the conjunctiva and tarsus, and a proliferating disease of

the connective tissue of the lid, presenting the picture of elephantiasis. Because other evidence of von Recklinghausen's disease had so far been missing, a further thorough examination of the skin was made, and this revealed two deeply situated nodules over the scapula and another deep in the bicipital fossa. The former of these were examined histologically and proved to be neurofibromatosis.

OTO-RHINO-LARYNGOLOGY.

Incidence of Malignant Tumours of the Head and Neck.

NOAH D. FABRICANT (*Archives of Otolaryngology*, January, 1939) gives a statistical survey of 249 malignant tumours about the head and neck recorded in the department of otology, rhinology and laryngology of the University of Illinois College of Medicine in the seven years from July 1, 1930, to July 1, 1937. The largest number of malignant tumours invaded the larynx. Second in numerical significance are the tumours which invaded the nose and paranasal sinuses. Following closely are the invaders of the œsophagus, the tongue, the bronchi and the tonsils. Seventy *per centum* of the 249 cancers are listed as being of the squamous cell type; 8·7% were basal cell carcinomata, found chiefly about the eye, orbit and nose, 2·7% were transitional cell carcinomata; 2·7% were undifferentiated tumours, and 2% were adeno-carcinomata. The remaining types, including all the sarcomata, individually form less than 1% of the total. The heavy predominance of squamous cell carcinoma is manifested by the fact that 95% of the tumours invading the larynx, almost 97% of those invading the œsophagus, 100% of those invading the tongue, 55% of those invading the bronchi and the neck, and 90% of those invading the tonsils were of this type. Other favourite sites for squamous cell carcinoma, as revealed by the survey, are the pharynx, the jaw and, to a less extent, the mouth.

A Study of Presbycusis.

NOBLE H. KELLEY (*Archives of Otolaryngology*, March, 1939), in a study on presbycusis, attempts to investigate three problems: first, what loss in auditory acuity, independent of special pathological conditions, accompanies increasing age; second, how such auditory loss affects what is heard in a musical tone; third, how such a loss affects the perception of speech. The author concludes that hearing for the frequencies up to 1,024 cycles remains practically normal with increasing age up to 70. Between 70 and 80 the auditory loss at 1,024 is 14 decibels. At 50, presbycusis is already apparent for frequencies of 2,048 cycles and beyond. The higher the frequency, the greater is the auditory loss. Presbycusis for the high frequencies progresses with increasing age. The elimination of all frequencies above 4,000 cycles does not affect the experienced quality of a violin tone when heard by a person over 60 who manifests presbycusis. Such elimination definitely alters the character of the same tone heard in the normal ear. In the recognition of vowels the average person past 60 is not seriously handicapped except at a low intensity, ten decibels above threshold. In the recognition of consonants a person past 60 is inferior at all intensities to a person with normal hearing. At the intensity preferred by a person with normal hearing for ordinary conversation (38 decibels) the presbycusic person recognizes 75% of the consonants.

Radical Mastoidectomy.

NATHAN A. BOLOTOW (*Archives of Otolaryngology*, February, 1939) discusses the use of the radical mastoid operation in the treatment of the dangerous types of suppuration of the temporal bone. He concludes that when there is evidence of chronic suppuration of the temporal bone, which may produce complications potentially and seriously endangering the life of a patient, the eradication of such disease is of prime importance. The radical mastoidectomy, therefore, is indicated in those selected cases in which there are pathological changes that may lead to dangerous intracranial extension of infection. In all cases suppurative *otitis media* is accompanied by more or less impairment of hearing. Depending on the extent of involvement of the structures of the middle ear and on the degree to which the cochlea has been affected, the hearing may improve, become worse or remain unchanged after the radical operation. The impairment of hearing and, in some cases, the intracranial complications might be minimized or avoided by proper medical attention and timely surgical intervention in the acute stages of infection of the ear. It is important to bear in mind that non-dangerous types of chronic suppuration of the temporal bone at any time may become dangerous by ingrowth of epithelium forming cholesteatoma, bony involvement and extension to vital intracranial structures.

Bronchoscopy and Bronchial Neoplasm.

KURT BERLINER (*Journal of the Mount Sinai Hospital, New York*, May-June, 1939) reports a case of latent carcinoma of the main bronchus obscured by massive pleural effusion, and illustrates the value of bronchoscopy in diagnosis of the cause of a massive pleural effusion. His patient was a woman of thirty-six years of age, who complained of pain in the left side of the chest, dyspnœa and fever for three days. Examination revealed signs of a large effusion in the left side of the chest with moderate clubbing of the fingers and toes, and radiographic examination revealed a massive pleural effusion displacing the mediastinum to the right. The von Pirquet skin test elicited a positive result, but the sputum did not contain tubercle bacilli, and in view of the age of the patient, the recent onset, the presence of fever and the past history of tuberculosis during adolescence, a tuberculous pleurisy was suspected. Aspiration of the chest yielded 900 cubic centimetres of clear straw-coloured fluid of a specific gravity of 1022, containing 12,000 leucocytes per cubic millimetre, of which 95% were lymphocytes and in which no tubercle bacilli were found. After two weeks the patient was discharged, but subsequently was admitted to two other hospitals, where the same diagnostic investigations were made, but in no instance had a bronchoscopic examination been made. Nine and a half months after the first examination the author found that the patient had not lost weight, the cough had increased in severity and the temperature was 101° F. The effusion had persisted in the left side of the chest despite repeated aspirations, and the presence of a carcinoma was then first suspected. Radiographic examination then showed a large collection of fluid and air in the left pleural cavity, shrinkage of the left lung, and displacement of the mediastinum to the right. Several hundred cubic centimetres of blood-stained fluid were aspirated on two occasions, but no tumour cells were found in the exudate. Bronchoscopic examination revealed the presence of a hard, firm mass arising from the lateral wall of the left main bronchus below the upper lobe orifice, and biopsy revealed adenocarcinoma. The patient died two months later, but a *post mortem* examination was not made. In his commentary on the case the author states that neoplasms arising in the substance of the lung and those arising from the small or even the main bronchi do not give rise to cough as a predominant symptom, that the symptoms of the patient may be due to metastases, and that if these are in the pleura they may be manifested by a pleural effusion. The author insists that bronchoscopic biopsy is indicated in neoplasm of the main bronchi.

Psychological Effect of Laryngectomy.

LEROY A. SCHALL (*Archives of Otolaryngology*, October, 1938) discusses the psychological condition of patients who have been subjected to laryngectomy. He is of the opinion that for the properly selected patient, laryngectomy, when indicated, is not a prominent factor in precipitating the act of suicide or in causing mental derangement if no previous psychopathological state has existed. His experience with a fairly large group of these patients has convinced him that they are a most optimistic and cheerful group, neither objects of curiosity nor, in most cases, recipients of charity.

Special Articles on Civilian War Casualties.

IX.

THE MEDICAL TREATMENT OF GAS CASUALTIES.[1]

THE term "gas" in the title of this paper is used in a general sense, to include any chemical substance, whether solid, liquid, or true gas, which is employed as a weapon of war. Although this article is primarily concerned with treatment, a brief discussion of the physical properties and possible chemical reactions of "gases" is inevitable, since upon these properties and reactions certain of our protective and therapeutic procedures rest.

GROUP I. THE VESICANTS.

The vesicants may preferably be considered first in order that their importance may be emphasized. Two only are generally known; these are named respectively "mustard gas" and "Lewisite".

Mustard Gas (Dichlorethyl-Sulphide).

Characteristics.

At ordinary temperature mustard gas is a heavy, oily liquid. In the impure state (in which it was used during the War) it has a brown colour, like sherry. When thrown on the ground the liquid will remain for days, giving off a vapour which is so poisonous that exposure of a few minutes to a concentration of 1 in 1,000,000 is sufficient to cause serious symptoms. It has the following chemical formula: $(ClC_2H_4)_2S$. It may be rendered harmless by any one of three different chemical reactions, as follows:

Firstly, on contact with water, mustard undergoes hydrolysis, dihydroxyethyl-sulphide and hydrochloric acid being formed: $(ClC_2H_4)_2S + 2H_2O = (HOC_2H_4)_2S + 2\ HCl$. Dihydroxyethyl-sulphide is a non-toxic substance. At ordinary temperatures this reaction proceeds slowly. It is the reaction by which mustard thrown on the ground is eventually rendered harmless. At high temperatures this reaction is accelerated, and this is the reason why we may decontaminate clothes by boiling them.

Secondly, on contact with hypochlorites, including calcium hypochlorite (synonyms: chloride of lime, "bleach", bleaching powder) mustard is oxidized, dichlorethyl-sulphoxide and calcium chloride being formed. The sulphoxide is non-toxic. This is the reaction upon which our principal method of decontamination of roads is based. This reaction may evolve a great deal of heat.

Thirdly, on contact with a chlorinating agent, such as sulphur-dichloride (SCl_2) or dichloramine T., mustard undergoes chlorination. The resultant compound is non-toxic. Chlorinating agents are used in the treatment of the dermal lesions caused by mustard.

Mustard is practically insoluble in water, but is freely soluble in hydrocarbons of the petroleum series such as petrol and kerosene. It is also soluble in certain other organic solvents such as carbon tetrachloride, carbon disulphide, alcohol and acetone.

Mustard gas is so named possibly because of its smell, possibly because of its vesicant effect. It should not be confused with true, natural mustard oil, which is prepared from the seeds of black mustard and which is a cyanate.

Mode of Action.

The essential action of mustard gas is that it behaves as a chemical irritant, inflicting a local burn on any soft tissue with which it comes in contact. The suggestion has been made that the irritant effect is due to hydrolysis of mustard, which results in the liberation of hydrochloric acid within the living cell. Further work has disproved this.

The belief has finally been reached that the whole molecule of the gas exerts a direct, toxic effect upon the cell. There is little, if any, evidence that the action of the gas is due to its absorption and conveyance by the blood stream to parts remote from the point of exposure.

Preventive Treatment of Lesions Due to Mustard Gas.

The term "preventive treatment" as used throughout this article, whether in relation to the vesicants or to the lung irritants, refers to treatment which may be employed after exposure to the gas and prior to the appearance of the principal symptoms. No discussion of protective measures which may be employed prior to exposure will be included.

As a preventive treatment of poisoning by mustard gas the method of choice is thoroughly to rub into the affected area, for a minute or so, either "bleach ointment" or "bleach paste". "Bleach" (bleaching powder) will rapidly neutralize free mustard, but it will irritate the skin if left in contact with it. Therefore the ointment or paste should be removed before long. Care must be taken to prevent the access of "bleach" to the eyes. "Bleach" should not be used if erythema has already developed, since it will aggravate the condition.

"Bleach ointment" is made by the mixing of equal parts, by weight, of "bleach" and white petroleum jelly. The use of white petroleum jelly is essential. Yellow petroleum jelly may contain impurities which the "bleach" may oxidize; even, it is said, generating heat on storage.

"Supertropical bleach" is ordinary "bleach" stabilized by the addition of quicklime and fulfilling certain conditions as regards its content of chlorine. It is intended to be less irritant to the skin than is ordinary "bleach". It may be used in place of, and in preference to, ordinary "bleach". "Bleach paste" may be made by the mixing of "supertropical bleach" to a creamy consistency with water.

If neither "bleach ointment" nor "bleach paste" is available, kerosene or petrol or another of the above-mentioned solvents of mustard may be applied. They may be applied to the affected area on swabs, and by firm and repeated rubbing mustard which still lingers on the skin may readily be removed; but it must be remembered that these materials merely dissolve mustard, they do not neutralize it, and therefore they must be allowed to come into contact neither with the fingers of the operator nor with an uncontaminated part of the skin of the patient.

Whether one uses bleach or one of the above-mentioned solvents, one should complete preventive treatment by subjecting the patient to a prolonged copious shower bath of hot water, employing much soap.

It will be noted that one speaks of the "affected area" readily enough. It is, however, very difficult to determine the limits of that area. If the brown stain of liquid mustard can be seen, it is known that the underlying skin is necessarily contaminated; but the area affected by the vapour is not always known. In such circumstances one should administer the shower bath which I have mentioned.

The only preventive treatment that may be applied to the eyes and the upper respiratory passages is to irrigate them repeatedly with a bland lotion such as normal saline solution.

The Effects of Mustard Gas Upon the Eyes.

Symptoms usually commence from two to eight hours after exposure to the gas. Then there occur pain and lachrymation. The conjunctiva becomes congested, and may indeed swell so that it projects in folds below the upper lid and above the lower lid. This swelling, together with swelling and spasm of the lids, causes a temporary blindness; photophobia is intense. Before long a mucopurulent conjunctivitis develops.

In persons severely burned there will be observed on the first day after exposure a dead white band crossing transversely the exposed area of the conjunctiva, whilst the areas protected by the lids above and below this band are injected and œdematous. The white band is due to coagulative œdema which compresses the vessels and threatens the nutrition of the cornea. At first it might be imagined that the white area represented a part less severely burned, while the upper and lower areas were

[1] A lecture delivered under the auspices of the Melbourne Permanent Post-Graduate Committee on August 3, 1939.

more severely burned. This, of course, is not so; the upper and lower areas, being partially protected by the lids, have suffered less severely.

The affected portion of the cornea is grey and lustreless; this is due to œdema of the epithelium and, later, to actual exfoliation of cells. Ulceration of the cornea may develop. In very rare instances of severe burning hypopyon may supervene.

As resolution occurs the œdema which caused the dead white band disappears, leaving the conjunctiva reddened. On the other hand, the vascular injection beneath the lids, above and below the white band, vanishes, so that the entire picture is changed, those parts of the eye which were red now being white and those which were white being red.

The recovery of 90% of persons affected will be complete within six weeks. It is recorded that of all the British soldiers in France only 14 suffered gross permanent impairment of vision, and of those only four contracted panophthalmitis and suffered removal of an eye.

Treatment of Ocular Lesions Due to Mustard Gas.

The treatment of lesions caused in the eyes by mustard gas is as follows: bathe the eyes repeatedly with a bland lotion such as normal saline solution or an aqueous solution of sodium bicarbonate (2%). Drop in sterile liquid paraffin to prevent adhesion of the lids. Failing paraffin, castor oil may be used; but it is slightly irritating. Shade the eyes, but do not bandage them. Bandaging implies pressure, and pressure is anathema to the lesion caused by mustard gas.

Though pain is severe the temptation to use cocaine should be resisted, for cocaine encourages exfoliation of the corneal epithelium.[1]

Instead one should employ atropine, either in the form of lamellæ, or preferably as a sterile (1%) ointment, repeating it every twelve hours in order to diminish reflex irritation of the iris and ciliary body. One should persist with atropine until the acute stage has passed, even, it is said, until the cornea has regained its normal lustre.

When the discharge from the eyes becomes mucopurulent a weak antiseptic solution should be instilled three times a day. The solution which is recommended by authorities overseas for the purpose is argyrol, in a concentration of 2% in water. This recommendation emphasizes how weak is the concentration in which one should use antiseptics when combating sepsis in lesions due to mustard gas.

Being interested to learn whether argyrol in a strength of only 2% had any antiseptic effect whatever, I had it tested by a bacteriologist skilled in the comparison of antiseptic agents. He found that argyrol in this concentration had considerable antiseptic effect. Even when the medium employed contained serum—a circumstance which militates against the efficacy of an antiseptic—the argyrol in a concentration of 2% killed a culture of *Staphylococcus aureus* in twenty-four hours.

An Australian ophthalmic surgeon of considerable military experience, discussing this matter, was inclined to discourage the use of argyrol, since it is a suspension. He stated that particles might be imprisoned by the healing epithelium, causing pigmentation. He preferred to recommend, as an antiseptic wash for the eye burned by mustard gas, acriflavine in a concentration of 1 in 5,000 in water. I therefore had this solution also tested by the bacteriologist, who ascertained that the antiseptic action of acriflavine in the concentration mentioned was not so effective as was that of a 2% solution of argyrol. Moreover, certain authorities overseas have accused acriflavine of being mildly irritant. Fleming[(1)] records that even in a concentration of 1 in 3,200 it will agglutinate red blood corpuscles. Therefore, taking all things into consideration, I do not feel entitled to depart from the conservative overseas recommendation to use argyrol in a concentration of 2%.

As an alternative Vedder[(2)] quotes Warthin and Weller as recommending highly the use of dichloramine T, 0·5% to 1% in chlorcosane, as not only preventing the eyes from becoming sealed but also preventing infection.

[1] One may, however, according to Muntsch,[(4)] an acknowledged German authority, use without hesitation "Novocain" in a 2% solution, to which may be added 5% of adrenaline (1 in 1,000 solution).

When the acute stage has passed one may dispense with the use of atropine, and one should then instil three times daily at some time other than those times at which the antiseptic is being applied the following astringent solution:

Boric acid, 10 grains.
Zinc sulphate, 1 or 2 grains.
Adrenaline (1 in 1,000), 0·5 or 1 drachm.
Water to the ounce.

Should ulceration of the cornea occur, bathe the eyes even more frequently and apply hot applications over the closed lids four times a day. If the ulcer becomes infiltrated it should be cauterized by the light application of pure carbolic acid put on with a nearly dry brush slightly moistened with the liquid. If hypopyon supervenes Saemisch section may be required.

As the patient recovers, a functional photophobia may supervene. On this account one must take the patient's shade from him as soon as the organic condition of the eye warrants that action. The patient may give up his shade only with the greatest reluctance.

Within the last few years reports have appeared in the literature of keratitis having recurred in certain soldiers burned nearly twenty years previously. This keratitis is intractable.

The Effects of Mustard Gas Upon the Respiratory Tract.

The mucous membrane of all the air passages may be affected by mustard gas, from the nostrils to the finest bronchioles. The lesions may vary from a slight catarrhal inflammation to a sloughing of the whole membrane. Sometimes a slough will be expectorated in the form of a cast of the bronchial tree. At autopsy the lung on section will be found to contain areas of emphysema alternating with patches of collapsed lung and with small visible hæmorrhages. The alveolar spaces, however, are dry, contrasting with their flooded condition in poisoning by the lung irritant gases.

The great danger to the patient consists in the development of septic bronchopneumonia. Because of this the majority of deaths occur on the fourth or fifth day after exposure.

Treatment of the Lesions Caused by Mustard Gas in the Respiratory Tract.

The naso-pharynx may be bathed with a warm solution of sodium bicarbonate (3%). For the larynx inhalations may be given of steam from a pint of boiling water containing a teaspoonful of a mixture of menthol (10 grains) in one ounce of compound tincture of benzoin.

The French authorities, alone, with the object of lessening the pain and danger of laryngitis, recommend strongly the following procedure. A powder is compounded thus:

Chlorhydrate of cocaine (powder).
Chlorhydrate of morphine (powder).
Of each 0·5 gramme.
Sugar of milk (powder).
Gum Arabic (powder).
Of each 5 grammes.

Of this mixture a piece the size of a pea is placed on a saucer. A hollow glass tube is bent in two places so that one end of it may be taken by the patient into his mouth reaching to the back of the tongue, and the other end may be placed on the powder which, being suddenly inhaled by the patient, enters his larynx.

In acute suffocative cases in which blocking below the larynx by sloughs or membranes was causing acute dyspnœa, the French injected an oil directly into the trachea by means of a fine needle inserted through the crico-thyreoid membrane.

To prevent bronchopneumonia the patient should be kept apart if possible from any infective pulmonary disorder, or indeed from any other source of pneumococci or virulent streptococci.

The use of the following mixture on a mask is recommended, partly as a prophylactic against infection and partly to ease the cough. The mask should be of gauze

spread on a frame. The mixture should be dropped on the gauze hourly:

Menthol, 20 grains.
Chloroform, 60 minims.
Creosote, 60 minims.
Oil of eucalyptus, 20 minims.
Rectified spirit to 1 ounce.

Treatment of an established bronchopneumonia follows the recognized rules including the employment of expectorants when the mucopus is tenacious. Venesection may, of course, be occasionally needed in the later stages; but it is not the essential effective therapeutic agent which it is for certain patients affected by the lung irritant gases. The same may be said of oxygen.

The Effects of Mustard Gas Upon the Skin.

As usual, there is a delay of at least some hours before symptoms appear. Then there will develop erythema, blistering, and later, septic infection with ulceration and necrosis. Subsequently reluctant healing will occur, frequently leaving pigmentation.

A mustard gas burn differs from a burn caused by heat in the following respects: the lesion develops more slowly; it is accompanied by a more intense inflammatory reaction and has a greater tendency to septic infection; there is a pronounced delay in the process of repair.

The mustard gas burn is as a rule extensive rather than deep. A burn as severe as the "third degree" is rare.

Treatment of Skin Lesions Due to Mustard Gas.

Treatment of skin lesions due to mustard gas is as follows. Evacuate the blisters by means of a sterile hypodermic syringe, allowing the epithelium to collapse and protect the raw surface below. This should be done within three hours of the formation of the blisters, even, on occasion, within two hours, otherwise the contained fluid will coagulate, become infected, and necessitate the total removal of the blister and its contents.

As a treatment for the fully developed burn when extensive, raw, intensely tender surfaces are exposed, the following is advised by an authoritative text-book:[9]

> . . . the use of a non-irritating antiseptic such as "Dettol", made by adding 20% by volume of "Dettol" to a freshly prepared 5% solution of tannic acid. After evacuating all blisters and removing the loose epithelium the solution is applied directly to the raw surfaces, either as a spray or preferably on lint, as a coagulum appears to form more quickly on a moist dressing than when an atomizer is used. Three or four layers of the lint are soaked in the mixture and applied to the burnt area, which is then covered lightly with cotton wool and a gauze bandage; the cotton wool and bandage may be removed every two or three hours, but the lint is left in position and is re-soaked. The entire dressing may be removed at the end of 8 to 12 hours, by which time a firm coagulum has formed. This is then spread with a 5% tannic acid solution and dried.

Now that is an occlusive dressing. It shuts the denuded surface in. A similar occlusive dressing, namely, "Ambrine", was given an extensive trial by all the nations concerned during the Great War and was abandoned. That being so, one may well ask why, when one occlusive treatment has admittedly failed, another should be expected to succeed; and I should prefer to recommend the treatment advised by the French,[9] German[10] and American[9] authorities, which implies the use of chlorinated antiseptics. The treatment is as follows: Prepare a quantity of Dakin's solution[1] of a strength of 0·54% of hypochlorous acid. Ring linen cloths out of this solution and place them on the denuded surfaces. Cover with wool, but do not bandage if this can be avoided. At intervals of thirty minutes moisten the linen cloths afresh. This moistening may be done either with the Dakin's solution again, or if that is too irritating with normal saline solution. Signs that Dakin's solution is too irritating are the causation of pain and the appearance of a white leathery glaze on the surface of the denuded area. Continue to use either saline solution or Dakin's solution throughout the day, the object being to exert a continuous antiseptic effect on the wound without hurting or harming the patient. Protect the neighbouring healthy skin from the discharges by "Vaseline" or preferably by one of the chlorinated creams hereunder mentioned.

As the night comes, remove the moist linen cloths and cleanse the wounds as far as possible, removing concretions and discharge. As a dressing for the night apply on gauze simply a bland ointment such as "Vaseline", or preferably a cream of the type of chloramine T. (1%) in sodium stearate surgical cream.

When the denuded surfaces are very large and pain is great the colloidal saline bath may be used. It is made thus:

Commercial corn starch, 1 pound.
Sodium bicarbonate, 1 pound.
Sterile saline solution, 20 to 30 gallons.
At a temperature of 90° to 95° F.

Suspend the patient in this bath on a canvas body cradle for from fifteen minutes to forty-eight hours. One must watch him lest his heart weaken.

If the above treatment is impracticable on account of the demands which it makes on the nursing staff, a simpler alternative treatment for denuded surfaces consists in the application on gauze or lint of dichloramine T. (1%) dissolved in the yellow oily semi-liquid chlorcosane. The above-mentioned chloramine T. (1%) in sodium stearate surgical cream may be used instead. These ointments need comparatively infrequent changing.

One wonders why "Ambrine" failed. Why should it retard healing of the lesion caused by mustard gas when it and similar occlusive agents are so successful in the treatment of ordinary thermal burns? Possibly traces of mustard linger in the tissues and, rising to the surface, exert a deleterious effect days after the patient is first exposed. The success of the chlorinating antiseptics may be partly due to the fact that they are capable of neutralizing any such traces of mustard.

General Treatment.

The diet should be light; fluids should be given freely. As convalescence proceeds one should take every care by suggestion and mental stimulation to avoid functional aphonia and similar after effects.

"Lewisite" (Chlorvinyldichlorarsine).

"Lewisite" is an arsenical vesicant made by passing acetylene through arsenic trichloride. It is, at ordinary temperatures, an oily liquid, and is intended to exert not only a vesicant action but also a toxic effect by absorption of arsenic. It has a blistering effect in a concentration as low as 1 in 3,000,000. Like mustard gas, it may be hydrolysed and oxidized. Like mustard gas, it is insoluble in water, but soluble in benzine and oils. The lesions which it produces vary only in small details from those produced by mustard, and the treatment, both preventive and curative, already described for lesions due to mustard gas is serviceable against those due to "Lewisite". Certain differences are, however, to be observed.

"Lewisite" hydrolyses much more readily than does mustard gas, especially in the presence of alkalis. On this account an admirable preventive treatment for the "Lewisite" burn is the application of sodium hydroxide (5%) in aqueous solution. This solution, of course, is itself irritant and must be soon removed.

Blisters formed by "Lewisite" should be evacuated immediately, since the fluid in them contains arsenic which may be absorbed. Whether or not the presence of arsenic in this blistering agent constitutes an increase in its efficacy as a warfare gas has yet to be learned. Experiments upon animals indicate that the absorption of arsenic which follows the application of "Lewisite" to the skin is

[1] To prepare Dakin's solution of this strength add to one litre of water 12·5 grammes of "bleaching powder". Shake vigorously. Add 12·5 grammes of boric acid powder and shake again. Allow to stand overnight and filter. The solution is now ready for use. It should be freshly made.

sufficient to cause significant accumulations of arsenic in the liver, kidneys and spleen.

"Lewisite", being first isolated and described in 1918, was not used during the Great War. The most favourable curative treatment is therefore partly a matter of conjecture. The Americans, presumably with the object of neutralizing arsenic, strongly advise the application to the burns of a ferric hydrate paste prepared thus:

> To a solution of ferric chloride slightly under the saturation point add strong ammonia little by little until a slight odour of ammonia persists. Do not stir, but place in deep narrow jars and allow the heavy chocolate coloured precipitate to settle to the bottom. Syphon off the supernatant fluid and refill with distilled water, repeating this washing until the fluid is free from chlorides as shown by giving no white precipitate on the addition of nitric acid and silver nitrate. The whole washing may require six to eight days. The fine colloidal non-granular ferric hydrate so obtained is strained on a filter and the thick paste is mixed in the proportion of six parts ferric hydrate to one of pure glycerine.
>
> The resulting smooth paste may be put up in impervious ointment boxes or collapsible tubes. It is very permanent when it is kept in air-tight containers.
>
> This paste is applied profusely over the burn and covered with oil silk, oiled paper, or other impervious dressing. The dressing may be renewed after about 12 hours. This paste may also be used to neutralize burns from liquid "Lewisite" immediately after they are received (Vedder[6]).

One must remark that the French official publication on the subject denies that this paste has any special virtue.

GROUP II. IRRITANTS TO THE LUNGS.

There is little essential difference between the actions of the various members of the group of lung irritant gases. All act by exerting a deleterious effect on the epithelium of the pulmonary alveoli, which results in the outpouring of copious fluid into the alveolar spaces.

As a representative of the group one may describe the most important and deadly member—phosgene. Phosgene is carbonoxychloride ($COCl_2$). It was first formed from carbon monoxide and chlorine under the influence of light. When inhaled it causes slight irritation to the respiratory passages, and there may be a delay of up to five hours before respiratory embarrassment is felt. Then there may occur sudden collapse and fit after fit of coughing, resulting in the coughing up of astonishing quantities of clear yellowish frothy fluid. Before long a true asphyxia develops, and this asphyxia may cause the patient to become either blue or grey. He may become blue and then grey and then die. He may, and frequently does, become grey first of all without passing through the blue stage. When once the grey type of asphyxia has well developed the prognosis is extremely grave; but with treatment recovery may yet occur. As a rule the "blue" patient tends to recover; but he may die, perhaps without passing through the grey stage at all.

J. S. Haldane has offered a partial explanation of the fact that one patient should become blue and another grey. He states that the "blue" patient, though, of course, lacking oxygen, is not suffering primarily from that lack, but rather from an embarrassment of the right auricle and ventricle, due to the difficulty which the heart finds in forcing the blood through the thrombosed capillaries which line the alveolar spaces in the water-logged lungs. The patient's blue colour is caused not only by the lack of oxygen in the arterial blood (it is practically venous blood), but also by an increase in the carbon dioxide in the circulation, which has caused an active dilatation of the superficial capillaries.

The "grey" patient, on the other hand, is not suffering from cardiac failure except in so far as the lack of oxygen naturally impairs the nutrition of the heart; rather is the "grey" patient in danger of respiratory failure. The salient feature of his pathological condition is not only that there has been obstruction to the intake of oxygen, but also, and more importantly, that there has been practically no limitation to the output of carbon dioxide. Carbon dioxide is far more soluble in water than is oxygen, and therefore carbon dioxide will pass out through the fluid in the alveolar spaces far more easily than oxygen can pass in. Thus the patient lacks the natural stimulus to the respiratory centre which an increase in carbon dioxide would supply. He is unable to breathe deeply. He is unable to make a fight to maintain his own breathing.

Other and variable physical factors play a part in this complex pathological condition. For instance, the diminution of carbon dioxide in the blood of the "grey" patient increases the affinity of hæmoglobin for oxygen. The hæmoglobin takes up oxygen from the air more readily, but parts with it to the tissues more reluctantly, which explains why the "grey" patient is not very apt to become blue but is very apt to die.

Treatment of Poisoning by the Lung Irritant Gases.

Preventive Treatment.

No greater mistake could be made than to regard the patient who has been exposed to a lung irritant gas as necessarily unaffected or slightly affected because he walks and talks without distress. Upon the care taken of the patient before his serious symptoms appear depends to a very great extent his ultimate fate. He should be a "stretcher case" from the moment exposure occurs. Rest and warmth were never more necessary. An attempt on the part of the patient to perform muscular work may result in a collapse which might otherwise never occur.

Curative Treatment.

A consideration of the pathological basis of the two different types of asphyxia above mentioned suggests at once an effective treatment for the patient who has become blue. His right auricle and ventricle may be relieved immensely by venesection. The withdrawal of from 15 to 20 ounces (450 to 600 cubic centimetres) of blood is as necessary and as effective as it could well be.

The outpouring into the alveolar spaces of the tremendous quantity of fluid drawn from the blood necessarily leaves the blood viscid and concentrated, so that the percentage of hæmoglobin is increased. It may reach 120% when estimated by the Sahli apparatus. Similarly, the erythrocyte count has been found to be over 9,000,000. The estimation of the hæmoglobin value is a guide not only to the prognosis but also to the treatment. If the venesection is followed, as it usually is, by a satisfactory drop in the content of hæmoglobin, all is well, and it will be found that the clinical symptoms are correspondingly relieved. If the hæmoglobin value increases again, a further venesection is indicated.

On account of the viscous nature of the blood, difficulty may be experienced in maintaining the flow. Vedder[6] has suggested that if the blood refuses to run normally saline solution may be infused into a vein in the other arm until the flow commences; but I should adopt this course reluctantly, if at all, since the intravenous injection of normal saline solution is in general contraindicated for these patients lest it encourage further exudation of fluid into the alveolar spaces. Venesection, as might be expected, does no good whatever to the "grey" patient, but rather harm.

Oxygen is invaluable in the treatment of poisoning by the lung irritant gases, whether the patient is blue or grey, whether he is affected mildly or severely. One should seek to tide the patient over the critical period, that is, over the first two or three days, and for this purpose oxygen should be administered almost continuously, preferably by means of a special oxygen mask.

Whether a mixture of oxygen and carbon dioxide would yield better results than oxygen alone is not known. For the "grey" patient such a mixture might be cautiously tried.

Major A. Stokes, R.A.M.C., introduced a simple method which enabled him to treat many patients simultaneously from one cylinder of oxygen without the need of attendants to hold masks. From a cylinder placed in the centre of a ward rubber tubes were led off, each ending in a

lubricated catheter, size number 8, which was introduced for four inches through the nose so that its end hung well over the soft palate, and through these catheters a continuous supply of oxygen was maintained. The patients were encouraged to breathe through the nose and not through the mouth.

Ancillary Measures to Combat the Pulmonary Œdema.

To Counteract the Immediate Effects of the Gas.—Damage is done by the intense acid reaction which is produced by phosgene in the pulmonary tissue. With the object of neutralizing this acid, inhalations of ammonia were tried, but failed; they actually acted as a further source of irritation. Since the Great War American workers experimenting upon dogs have found that injections of urease (a ferment that acts on the urea of the blood, liberating ammonia) exerts a beneficial action when injected intravenously immediately after exposure to the gas. Presumably the ammonia so produced is liberated directly into the tissues of the lung and thus neutralizes promptly a certain portion of the acid. The urease is prepared by means of a 10% aqueous solution of jack bean meal. The dosage for a man of average weight is about seven cubic centimetres of this solution, injected intravenously. The action of the urease may be hastened by the simultaneous injection of a few grains of urea.

To Diminish the Exudation of Fluid into the Alveolar Spaces.—It has long been known that ipecacuanha reduces pulmonary congestion and that emetine appears to have a constricting effect upon the pulmonary capillaries. Workers have recommended one grain of emetine as a suitable dose for a man of average weight who has been gassed by phosgene. Animals so treated have developed pulmonary œdema much more slowly than untreated animals.

To Increase the Colloids of the Blood.—Numerous experiments conducted at Edgewood Arsenal and elsewhere have shown that dogs may be safely given intravenous injections of an aqueous solution composed of 25% gum-Arabic with 25% glucose. Five cubic centimetres of this solution were injected slowly for each kilogram of body weight. It was found that if this injection was given soon after exposure to the gas (within one or two hours), dogs which had received an otherwise lethal dose might be saved by that treatment alone.

Therefore one may suggest that solutions of gum and glucose may be prepared and sterilized in advance in field hospitals or casualty clearing stations, or possibly even in first aid stations, since the equipment required is simple, consisting merely of a hypodermic needle of a fairly large bore, rubber tubing and an irrigator. The irrigator may be filled with the hot solution, the needle introduced into a vein, and the injection given slowly. It cannot be given rapidly, since it is so viscid. About twenty minutes should be used for the injection of the 350 cubic centimetres which one would administer to a man of average weight. One must, however, emphasize that this treatment, though supported by successful animal experiments, has not yet been used sufficiently upon human subjects to be recommended otherwise than as a possible experimental procedure.

General Measures in the Treatment of Patients Poisoned by Phosgene.

Adrenaline and pituitrin are contraindicated for patients poisoned by phosgene, since an increase in the blood pressure may encourage exudation of fluid into the lung. Paradoxically enough, amyl nitrite, which lowers the blood pressure, was also found to give unsatisfactory results. Artificial respiration is useless. Morphine has a bad effect.

After the acute stage has passed the patients should have careful nursing and watching for several weeks. There is always the possibility of infection and the development of bronchopneumonia. Prophylactic measures, such as cleansing of the mouth and isolation, naturally suggest themselves. As a rule, recovery, once it commences, proceeds without interruption. A certain proportion of patients develop disordered action of the heart and spasmodic nocturnal dyspnœa. For those suffering from disordered action of the heart graduated exercises are indicated. Those who suffered from nocturnal dyspnœa were greatly benefited by the administration of oxygen.

C. W. ADEY, E.D., M.D., M.R.A.C.P.,
Lieutenant-Colonel, A.A.M.C.,
Melbourne.

REFERENCES.

(1) A. Fleming: Quoted by W. H. Martindale and W. W. Westcott in "The Extra Pharmacopœia", Seventeenth Edition, Volume I, page 295.
(2) E. B. Vedder: "The Medical Aspects of Gas Warfare", 1925, page 154.
(3) C. Héderer and M. Istin: *"L'arme chimique et ses blessures"*, 1935, page 281.
(4) O. Muntsch: *"Leitfaden der Pathologie und Therapie der Kampfgaserkrankungen"*, 1932, page 68.
(5) E. B. Vedder: *Loco citato*, pages 155 and 156.
(6) E. B. Vedder: *Loco citato*, pages 164 and 165.
(7) E. B. Vedder: *Loco citato*, page 112.
(8) Air Raid Precautions Handbook Number 3: "The Medical Treatment of Gas Casualties", issued by the British Home Office.

British Medical Association News.

SCIENTIFIC.

A MEETING of the South Australian Branch of the British Medical Association was held on July 27, 1939, at the Adelaide Hospital. The meeting took the form of a number of clinical demonstrations by members of the honorary staff.

Dislocation of the Wrist.

DR. A. C. MCEACHERN showed a man, aged fifty-four years, who had sustained a dislocation of the wrist seventeen days previously. The initial skiagram had revealed a transscaphoid perilunar dislocation and fracture of the radial and ulnar styloids with gross displacement. Perfect reduction had been effected by traction and subsequent immobilization in plaster. Dr. McEachern said that Böhler described this as one of the types of dislocation around the lunate bone. Dr. McEachern emphasized the key position that was occupied by the joint between the lunate and the capitate, and expressed his belief in the view that a dorsal dislocation of the base of the hand over the lunate was the first stage in anterior dislocation of the lunate.

Adenoma of the Pituitary.

Dr. McEachern's second patient was a woman, aged twenty-three years, who had been married for sixteen months and had not become pregnant. She had suffered from frontal headaches for four weeks. Her weight was fifteen stone and had been exactly doubled in seven years. She had menstruated once when sixteen years of age; after four years of amenorrhœa menstruation had occurred more or less regularly for two years, and for the last four months there had been amenorrhœa. The systolic blood pressure was 140 and the diastolic pressure 90 millimetres of mercury, and a blood sugar curve revealed increased sugar tolerance. X ray examination revealed moderate enlargement of the *sella turcica*, and examination of the visual fields indicated slight pressure on the chiasma from below. Her condition was a typical example of a chromophobe adenoma of the pituitary. Dr. McEachern said that her visual fields would be examined every two months, and if the changes were progressive Dr. Lindon would explore the pituitary. Operation would not relieve the symptoms due to hypopituitarism.

Lesion of the Brachial Plexus.

The third patient shown by Dr. McEachern was a girl, aged fourteen years, who complained of a contracture of the right little finger associated with numbness, which had been slowly increasing for two years. Both little fingers were rather short. The right one was flexed at the interphalangeal joints and extended at the metacarpophalangeal joint. There was impaired response to light

touch over the whole of the little finger and on the ulnar border of the hand. Pronounced drooping of the right shoulder was present. The possibility of a cervical rib was excluded by X ray examination. It was suggested that this was a partial inner cord syndrome due to pressure on a normal first rib. The patient was being treated by physiotherapy, and it was thought that if the condition continued to progress exploration of the plexus would be indicated.

DR. M. ERICHSON said that such symptoms could be produced by syphilitic pachymeningitis.

Dr. McEachern said that his patients had been shown with the permission of Dr. Leonard Lindon and Dr. G. H. Burnell, and he expressed his thanks to them.

Dermatomyositis.

DR. M. T. COCKBURN showed a boy, aged four years and six months, who appeared to be suffering from dermatomyositis. The boy had not been well for about three months and had complained of vague symptoms, including loss of weight, anorexia and weakness. Latterly he had been noticed by his parents to complain of pain in his arms when being undressed; the parents had also noticed that he was not walking freely.

On examination he was found to have a temperature of 101° F.; the skin of the eyelids was distinctly mauve in colour, and the same colour was present over the metacarpo-phalangeal joints. The skin was inelastic, especially over the cheeks, and the substance of the cheeks was quite hard. The muscles of the limbs could not be fully extended at elbows and knees. The muscle power of the limbs was weak, and walking was performed with difficulty. The abdomen was greatly distended and a small umbilical hernia was present.

Microscopic examination of biopsy specimens of skin, subcutaneous tissue and muscle from the lateral aspect of the right thigh revealed lymphocytic infiltration in the muscle fibres and scattered collections of round cells near vessels. No definite muscle degeneration was detected. Dr. Cockburn remarked that a detailed account of the case would be submitted later.

Fröhlich's Syndrome.

Dr. Cockburn's second patient was a boy, aged six years, who showed mental backwardness, adiposity and hypogenitalism, with complete absence of testes outside the abdominal cavity, and a pigmented area of skin with transverse rugæ, which represented the rudimentary scrotum.

Papulo-Serpiginous Syphilides.

DR. W. C. T. UPTON showed a female patient, aged forty years, suffering from papulo-serpiginous syphilides. The patient stated that eight months earlier she fell, injuring the skin on her forehead. A rash appeared, which gradually spread. The patient had one child and had had no miscarriages. A lesion had appeared on the left cheek two months after the appearance of the skin lesion. The patient stated that the initial lesion was a small white pimple. The Wassermann test elicited a positive reaction.

Dr. Upton remarked that a papulo-serpiginous syphilide was a gummatous lesion confined to the dermis, as opposed to the typical gumma of the subcutaneous tissue. Lesions of this type usually occurred from two to ten years after the primary infection.

Granuloma Annulare.

Dr. Upton then showed a male patient, aged thirty-eight years, suffering from *granuloma annulare*. An eruption had occurred on the patient's hands twelve months earlier; it had cleared up spontaneously and had recurred a few weeks prior to the meeting.

Dr. Upton said that the condition usually began as a small semi-translucent nodule about the size of a boiled sago grain. The lesions formed rings or crescents, and usually appeared on the hands, legs, feet or face. The exact cause was not known. Some authorities thought that the condition was a tuberculide, but there was slight evidence to support that view. Sometimes the lesion disappeared spontaneously, and it usually responded to X ray therapy.

Sycosis Coccogenica ("Barber's Rash").

Dr. Upton finally showed a man, aged thirty years, suffering from *sycosis coccogenica*. The eruption had begun on the shaving area some years earlier and had gradually spread until it involved the whole of the shaving area of the face and neck. The patient had for three years had the lesion as it appeared at the time of the meeting. Dr. Upton said that the disorder was usually difficult to cure when it was of such long duration, although X ray therapy was often successful. "Quinolor Ointment" (Squibbs) was sometimes of great help, especially in the early stages. In the case under discussion "Quinolor Ointment" had been in use for two weeks only, and the improvement up to the time of the meeting was only slight.

Renal Carcinoma.

DR. W. JOHN CLOSE showed a patient who had been operated on by the abdominal route twenty-four days previously for renal carcinoma. Dr. Close also showed pyelographic films and a pathological specimen; in the film a pronounced filling defect was revealed.

Dr. Close also showed two other specimens with their respective pyelograms for the purpose of contrast. In one series of pyelograms a typical "spider-leg" deformity was revealed, and in the other the appearance was of the "crushed spider" type.

Jejunal Fistula.

Dr. Close also showed a patient who had been treated as a "surgical emergency" eleven weeks previously; a diagnosis of acute intestinal obstruction had been made at that time. A loop of gangrenous bowel, 18 inches long, had been resected; at the operation dense adhesions of small intestine had had to be separated. Dr. Close said that apparently some devitalization had taken place, and five days later very irritating jejunal contents had been poured out. The skin of the abdominal wall and the vulva and buttocks soon became excoriated, and it was necessary to improvise a complicated plumbing system for three purposes: (i) to suck out the duodenal contents through a catheter passed down to the duodenum *per nares*, (ii) to suck the wound dry by the continuous employment of a dynamo pump, the tubing being anchored in the wound by a mass of beef steak, and (iii) to provide fluid, sodium chloride and glucose, by means of the continuous intravenous drip method. Dr. Close said that the skin had recovered sufficiently to allow of a secondary operation. This had been only partially successful; but the discharge was slight, was decreasing in amount, and was easily absorbed by kaolin.

Mixed Tumour of the Parotid.

Dr. Close then showed a patient who had recently undergone operation for mixed tumour of the parotid. A photograph had been taken prior to the operation; this revealed an elongated mass, eleven inches in length, attached to a base extending from the pinna almost to the clavicle. Examination of a section of the growth revealed a glandular mass; the pathologist reported it to be a carcinoma, with patches of mucin, but no hæmorrhages or cartilage. The history of the lesion was of twelve years' duration, and growth had been more rapid during the last two years. Slight interference with the facial nerve had occurred, but there had been no lymphatic metastases.

A Case for Diagnosis.

The fourth patient shown by Dr. Close was a woman, suffering from what was thought to be a lipoma of the breast. Dr. Close said that he showed the patient because the lesion was a rarity, and for the purpose of diagnosis. The growth was a soft circumscribed lump, the size of a duck's egg, occupying the lower portion of the breast; it had been present for two years.

Subdural Hæmatoma.

DR. D. G. MCKAY showed a male infant, aged one year. The child's birth had been a breech delivery, without difficulty. On the fourth day of life the child had begun to have fits involving the right side of the face, the right arm and the right leg. The fits consisted of tonic and clonic spasms of these areas, and the head and eyes were turned to the right.

General examination at that time had revealed that the baby was drowsy and pale and had an icteric tinge. The fontanelle was bulging and very tense. The right arm and leg were slightly spastic.

On July 19, 1938, the subdural spaces were explored with a large-bore needle inserted at the lateral angles of the fontanelle. Thirty cubic centimetres of blood were removed from the left subdural space and five cubic centimetres from the right. On July 27 the child had further fits, and five cubic centimetres of blood were removed from the left subdural space and 0·5 cubic centimetre was removed from the right. On July 22, further fits having occurred, three cubic centimetres of blood were removed from the left subdural space. On July 24 the child had another fit, and two or three cubic centimetres of blood were removed from the left subdural space. On July 27, no further fits having occurred, two cubic centimetres of old blood were removed from the left subdural space. On July 31 blood appeared in the child's stools, and 25 cubic centimetres were removed from the left subdural space. On August 3, 15 cubic centimetres of old blood were removed from the left subdural space. On August 4 the child was given a transfusion of 90 cubic centimetres of the father's blood. On August 5 the left subdural space was explored and about one cubic centimetre of blood was removed. On August 8 the fontanelle was flat and no blood was obtained from the left subdural space. The baby appeared quite normal; the circumference of his head was 14·5 inches. On July 26, 1939, the child was aged one year and was apparently normal. He had mild alternating strabismus. The circumference of his head was 17·5 inches. No spasticity was present, and the child's mental development was above the average.

Talipes Equino-Varus.

Dr. McKay next showed a male infant, aged seven months. When the child was born in December, 1938, a fair degree of equinus had been present; the fore part of the foot had been considerably adducted, and pronounced inversion of the heel with a well-defined crease had been noticed. The foot was manipulated under general anæsthesia on February 18, 1939, and a hobble splint was applied. The splint was removed, the foot was manipulated without anæsthesia, and the splint was reapplied at weekly intervals until March 28, 1939, when the splint was discarded. From then until June 13, 1939, the foot was manipulated at weekly intervals and maintained in position by means of strapping. The leg became rather excoriated, so a plaster spica was applied on June 13 and removed on July 25. Dr. McKay said that the patient was still under treatment at the time of the meeting.

Complete Hare Lip and Cleft Palate.

Dr. McKay finally showed a female, aged two years and four months, suffering from complete hare lip and cleft palate. On June 15, 1937, the lip had been repaired by means of the Blair and Brown modification of the Mirault operation. The anterior portion of the palate was closed according to the Veau technique. The operation was performed when the child weighed approximately ten pounds and was gaining in weight. On November 14, 1938, the posterior palatine arteries were divided. On April 3, 1939, the repair of the palate was completed by Dennis Browne's modification of Langenbeck's operation; at that time the child was approximately two years old.

Disordered Heart Sounds.

DR. E. F. GARTRELL showed three patients with triple heart sounds, in order to emphasize the necessity for differentiating true gallop rhythm from the so-called reduplicated sounds. He pointed out that the former was frequently associated with *pulsus alternans*, and that in a series of cases the average duration of life subsequent to the detection of gallop rhythm was eighteen months, whereas reduplicated sounds were far less significant.

Dr. Gartrell's first patient was a female, aged thirty-eight years, who had suffered from kidney trouble and high blood pressure during pregnancy four years earlier. She subsequently developed increasing breathlessness on exertion and eventually some visual disability.

On examination some swelling of the disks and œdema of the dependent parts were revealed; the systolic blood pressure was 250 and the diastolic pressure 140 millimetres of mercury. The first sound at the apex was reduplicated and the second sound in the aortic area was high pitched. The electrocardiogram revealed a bundle branch lesion of the common type. The blood urea concentration did not rise above 1·2%.

The second patient shown by Dr. Gartrell was a female, aged fifty-seven years, who had been admitted to hospital complaining of increasing breathlessness on exertion for a period of twelve months, and latterly some substernal pain and tightness on exertion.

On admission to hospital the patient's pulse rate was 40 per minute; this was due to 2 : 1 heart block with a very long *P-R* interval. The auricular sounds were audible just internal to the apex.

Subsequently the pulse became irregular, owing to the presence of ventricular premature beats. After the administration of ephedrine, three-eighths of a grain twice a day, the *P-R* interval became shorter and the pulse rate was doubled, owing to the absence of dropped beats. The intraventricular block, however, still persisted. The presence of auricular sounds now gave the impression of triple rhythm.

Dr. Gartrell's third patient was a man, aged fifty-one years, who had had breathlessness on exertion, steadily increasing for a period of two years. For twelve months he had had some œdema and recently this had become excessive, necessitating the injection of "Salyrgan". This had been at first efficacious and had removed his ascites. Subsequently it lost its effect and had to be replaced by "Novurit", which was also effective for a time. After this, "Neptal" was quite effective.

Dr. Gartrell said that during the last three months the man had exhibited varying degrees of true gallop rhythm accompanied by *pulsus alternans*. The outlook was very grave.

The Royal Australasian College of Physicians.

OPENING OF THE COLLEGE BUILDING.

A MEETING of the Royal Australasian College of Physicians was held in Sydney on September 8 and 9, 1939. This meeting marked the occasion of the opening of the college's own building at 145, Macquarie Street, Sydney. Fellows and Members from every Australian State were present and the scientific sessions were largely attended. In view of the national situation, the council had decided earlier in the week that the late afternoon party previously planned for the first day of the meeting would not be held—a simple inspection of the building by members and their wives being substituted—but in other respects the programme was carried out as arranged.

A council meeting was held on the morning of September 8, followed by a luncheon, at which over 100 Fellows and Members were present. In the afternoon the first scientific session was held in the Stawell Hall. The President, Sir Charles Blackburn, in welcoming those present to the first meeting held in this hall, said that at last a dream was realized, and he was proud to have the honour of presiding at this the first official gathering of the college in its own home. He then outlined the chief events which had occurred in the progress of the college since

the annual meeting in Melbourne in March, especially with regard to some important alterations in the constitution, which had been approved at the general meeting in Sydney last year and which now had been assented to by the Governor-in-Council and finally approved by order of the Supreme Court, and also the petition for a royal charter, which had now reached a final form and with which successful progress was being made. Sir Charles Blackburn then informed the meeting that joint action had been taken by the Royal Australasian College of Physicians and the Royal Australasian College of Surgeons to offer all assistance possible to the Australian Government in the present national emergency. A letter had been sent to the Prime Minister assuring him of the cooperation of the college, offering assistance in the securing and maintaining of specialist medical services both for home and military service, and also offering the use of the buildings and personnel of the Royal Australasian College of Physicians in Sydney and the Royal Australasian College of Surgeons in Melbourne. The action of the President in thus pledging the college to assist in national service was unanimously endorsed by the meeting.

The programme for the first scientific session was as follows:

1. "The Clinical Value of the Lead IV *R* in the Electrocardiogram", Dr. Ellis Murphy.
2. "Allergy", Professor H. K. Ward.
3. "Besnier-Boeck's Disease", Professor C. G. Lambie, Dr. A. H. Tebbutt.
4. "Encephalography", with film demonstration of technique, Dr. E. Graeme Robertson.

Dr. Ellis Murphy was unfortunately unable to be present, owing to his having been mobilized for military service; but the subject of his communication was discussed by a number of others.

The Royal Australasian College of Physicians, Sydney.

At 5.30 p.m. there was an official inspection of the building. This function was arranged for Fellows and Members with their wives or other relatives, and the President of the New South Wales Branch of the British Medical Association, Dr. G. M. Barron, and Mrs. Barron were present by invitation.

On Saturday, September 9, the second scientific session was held in the Stawell Hall, the programme being as follows:

1. "A Survey of Some Unusual Renal Lesions Associated with Vascular Hypertension", Dr. A. J. Canny.
2. "Neuro-Muscular Disorders in the Light of Recent Physiological and Pharmacological Investigations", Dr. J. C. Eccles.
3. "Soldier's Heart—Twenty Years After", Dr. Ralph Whishaw.

As a result of a discussion on soldier's heart and, in particular, on neuro-circulatory asthenia, it was resolved by the meeting that the council should arrange for the preparation of a special report on this subject, which could be transmitted to the military authorities, as it was felt that an authoritative statement would prove to be of great value in future military medical work. The necessary action was taken subsequently by the council.

The Council of the Royal Australasian College of Surgeons had met in the library of the college on the morning of September 9, and, at the suggestion of the President and Council of the Royal Australasian College of Surgeons, a joint meeting of the councils of the two colleges was arranged for the afternoon. The Council of the Royal Australasian College of Physicians entertained the members of the Council of the Royal Australasian College of Surgeons at luncheon, after which the two councils met in the library of the Royal Australasian College of Physicians to discuss matters of mutual interest. At this meeting important matters concerning postgraduate work and the organization of specialist services during the war were discussed, and it is confidently believed by the councils of both colleges that the close and friendly cooperation evidenced in this the first joint meeting of these related bodies will have the most important influence upon medical and surgical practice in their relation both to the general public and to the service of the nation.

On Tuesday, September 12, the New South Wales executive of the council of the college entertained those benefactors whose generosity has made possible the purchase, adaptation and equipment of the permanent headquarters of the college in Australia. The guests included representatives of the New South Wales Government and many prominent citizens and their wives who had rendered service to the college. After being received by the President, the guests were entertained at afternoon tea and conducted over the building.

The College Building.

In securing for its headquarters 145, Macquarie Street, Sydney, the Royal Australasian College of Physicians entered into possession of a building which not only readily lent itself to adaptation for the special purposes of such a body, but was also historically interesting and intrinsically full of the character and dignity of its period. Originally built by the late John Fairfax, it was for a number of years the home of the Fairfax family and later was acquired by the Warrigal Club. Known as the home of this club for half a century, the building was, after a brief interregnum, purchased on behalf of the Royal Australasian College of Physicians through the generous financial assistance of the New South Wales Government, a number of citizens who were interested in assisting to secure a permanent home in Sydney for the college, and many of the New South Wales Fellows themselves.

The Government architect, Mr. Cobden Parkes, drew up the plans for alterations and additions. The constructional work was supervised by his department, and the college is greatly indebted to Mr. Collier in particular for his great personal interest and help in this work. The contract was carried out by Mr. J. G. Taylor. A hall, capable of seating nearly 200 persons in comfort, has been added to the rear of the property without alteration of the essential character of the building. The original façade has been preserved with little change. The iron columns have been sanded so that they accord well with the stone structure of the lower two floors, and the old cast iron balcony railings have been replaced by wrought iron railings of special design on all three balconies, which run the complete width of the building. The choice of an effective shade of blue for the front doors and the shutters, and a warm red-brown for the railings has lightened the exterior without any loss of character. A plain stone wall encloses a lawn bisected by the stone entrance steps leading to the veranda, and two Lombardy poplars, the gift of one of the Fellows, replace the old palms which grew so long in front of the Warrigal Club.

Library of the Royal Australasian College of Physicians.

The ground floor houses the office and assembly rooms of the college, and the library occupies the entire front of the building on the first floor. The upper floors are not required by the college at present and are let for residential purposes. The entrance hall is guarded by glass doors, which bear the device of a hand grasping the Æsculapian rod, with its twined serpents, this being incorporated in the arms of the college. On the left hand is a spacious reception room, comfortably furnished with large lounge chairs, a cabinet and writing table, made of Queensland blackbean with ribbon maple inlays. Behind this room are cloak rooms. Opposite to the reception room is the general office, opening out of which is the secretary's room. All the interior decorating has been carried out by Mrs. Gunz, who not only planned the colour schemes and selected the materials, but also designed the furniture. Where possible, the original cedar fittings have been retained and the cedar doors, skirtings and shutters on the ground floor and a cabinet in the rear part of the hall have been carefully treated so as to restore their pristine beauty. The graceful spiral staircase leading from the entrance hall has also been left untouched, and its effect is enhanced by a stained glass window embodying the arms of the college and its motto, "*Hominum Servire Saluti*". This window bears the emblematic bird of South Australia, being the gift of the Fellows of that State. The modern purpose of the building is aptly expressed in the designs and colours used in furnishing. Two tones of blue in the hide of the chairs in the front rooms contrast strikingly with a primrose shade used for some of the chairs in the reception room, and the warm cinnamon tints of the carpets accord well with the Italian damask curtains. Australian woods have been used throughout. The office furniture is striking and ingenious. The large desks are of Queensland beech with bases of Queensland cedar and dull chrome fittings, and these match a specially designed suite of cupboards flanking two walls, which contain and conceal steel office furniture of modern type. Such utilitarian articles as a safe, filing cabinets and even telephone exchange board are thus disposed of in such a fashion that, while readily accessible, they form part of a concerted and artistic design.

The library, which is also designed to be used as a council room, occupies the front of the first floor, and behind this are a librarian's room and a smaller room, which may be used as a store room and is well adapted for the display of scientific exhibits. The library is panelled in Tasmanian blackwood and, like the whole of the rooms on the ground floor, is close carpeted. This room is well lit by large full-length windows, which open onto the balcony overlooking the Botanical Gardens, and the specially chosen chenille curtains are so designed as to repeat the light green shade of the roof, so that the artificial lighting is particularly soft and pleasing. The retention of the original shutters in the library has helped to preserve the spirit of the old building. The magnificent table, as its inlaid inscription shows, is the gift of the Royal Australasian College of Surgeons. It is really a combination of movable tables, fitted together to make a long horseshoe shape; the wood is Tasmanian blackwood with inlays of Queensland ash. Large hide-covered chairs are provided, and a special president's chair stands at the head of this council table, carved with the college arms and displaying the emblem fern leaves, which indicate its origin, as it is the gift of the New Zealand Fellows.

The assembly hall is at the rear of the building, on the ground level, and is reached through a short corridor panelled in Putts pine. This panelling, continued flush over the lift well, gives a specially cheerful character to this lobby—a spirit accentuated by the addition of a lounge seat upholstered in scarlet leather.

The Stawell Hall is named in memory of the late Sir Richard Stawell, who was the first president of the Association of Physicians of Australasia, and over the dais is the inscription "Stawell Memorial Hall". Just within the entrance is a bronze plaque of Sir Richard Stawell, the gift of Sir Charles Blackburn, the first President of the college. This hall is specially designed for scientific meetings. The dais is placed across one angle and the seats are placed radially on each side of two aisles, sloping towards the front. The seats are individual theatre seats upholstered in hide over "Latex" rubber, and an interesting colour scheme is used in the upholstery, the back rows being brown, and the rows nearer the front two tones of

red. The blue curtains are lined to exclude daylight when necessary, and artificial lighting is by three banks of multiple reflector lights in the ceiling behind glass panels of special moulding and colour. On the platform are three large red hide-covered chairs and a long table of Queensland walnut. The same wood is used for the cover for a wash-basin near the dais, and for a specially designed adjustable lectern, the gift of Mrs. Mathison, of Melbourne, in memory of her late son. The entire hall is panelled to a height of seven feet with Putts pine over a walnut base, the doors and surrounding panels being walnut, and the flooring is cork, ensuring quietness and good appearance. At the back of the hall is a balcony used for cinematograph projection; the screen is behind the dais and can be adjusted as to angle and also raised to disclose a blackboard. The projection apparatus is contained in a pit immediately in front of the platform, which is fitted with a pneumatic hoist, so that the whole may be sunk below floor level when not in use. The design is such, however, that the view of everyone in the hall is clear even when the apparatus is in use. The equipment is by Zeiss, and includes an episcope for diagrams, pictures and specimens, an X ray diascope, a lantern for slides and a microprojection apparatus, the latter supplied with four grades of magnification, the highest of which is a new type of aplanat lens, which gives an absolutely flat and brilliant field. Provision has been made for the installation of benches or tables at either side of the projection pit, and both gas and power and lighting points are available if required. Adequate ventilation of the hall is assured by the use of a pressure system. Filtered air, which may be warmed at will, is pumped through vents in the ceiling and makes its exit through mushroomed domes under the seats. All the clocks in the building are electric in type. This hall, in point of design, comfort, acoustics and scientific equipment, admirably fulfils every purpose.

There is a roomy basement in which all the machinery is housed and where there are also a kitchen and storeroom for crockery *et cetera*. Provision has also been made for a photographic room if photostat service is ever required for the library. In general the building is a successful compromise between the preservation of an earlier style in local architectural history and adaptation to modern requirements. In the long row of professional and other buildings along the western side of Macquarie Street it is the sole remaining structure of its period, and it admirably reflects the tradition which it now represents. It is complementary to the splendid modern building of the Royal Australasian College of Surgeons in Melbourne, and the completion of the central quarters of these two colleges will surely mark the beginning of a still greater advance in medical knowledge and attainment in Australia and New Zealand.

Correspondence.

THE CONTROL OF PUBLIC HOSPITALS AND THE NORTH SHORE HOSPITAL INQUIRY.

SIR: The excellent editorial on hospital administration and the North Shore Hospital in the issue of November 11 would have been even better if the reference to ministerial action had been omitted. That the Minister or Commission could interfere with a corporate body, such as the Board of Directors, without any charge being made would be a bad principle to introduce into hospital management. Mr. FitzSimons has been unjustly criticized for not taking earlier action. The facts are that no public charge was made against the board, and the legal opinion of the Crown Law Office and a senior member of the Bar was that it had acted within its rights. Later, when the Vigilance Committee made a direct charge against the board, the acting Minister, Mr. Richardson, was justified in instituting a full inquiry. Mr. FitzSimons, had he been in Sydney, would have acted similarly. Let us hope it will never come to pass that a Minister of Health or the Commission will ever be guilty of interfering with the management of our hospital boards unless a direct charge is made against them.

Yours, etc.,

HERBERT H. SCHLINK,
Chairman of the Board of Directors,
Royal Prince Alfred Hospital.

Sydney,
November 20, 1939.

Naval, Military and Air Force.

APPOINTMENTS.

THE undermentioned appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Number 146, of November 23, 1939.

AUSTRALIAN MILITARY FORCES.

Australian Army Medical Corps (Permanent).

To be Captain (provisionally)—John Robertson Nimmo, with pay at the rate of £750 *per annum*, rising by annual increments of £50 to £900 *per annum* (subject to variation in accordance with variations in the cost of living in the manner prescribed by regulation 27 of the Military Financial Regulations), inclusive of all allowances except travelling allowance, to date 6th November, 1939; appointment to be for a period of two years subject to reappointment.

NORTHERN COMMAND.

First Military District.

Australian Army Medical Corps Reserve.

To be Honorary Captain—Norman Geaney, 18th October, 1939. *To be Honorary Lieutenant*—John Bingham Sheridan Stable, 10th October, 1939.

EASTERN COMMAND.

Second Military District.

Australian Army Medical Corps.

To be Captains (provisionally) supernumerary to establishment pending absorption—Robert Frederick Matthews and Leo Vivian Armati, 23rd October, 1939; Captain (provisionally) W. H. Neild is brought on the authorized establishment, 22nd October, 1939.

SOUTHERN COMMAND.

Third Military District.

Australian Army Medical Corps.

Honorary Captain I. Le Souef is appointed from the Reserve of Officers (A.A.M.C.) and to be Captain (provisionally) supernumerary to establishment pending absorption, 10th October, 1939; Captain A. R. Buchanan is transferred to the Reserve of Officers (A.A.M.C.), 22nd October, 1939.

Award of the Australian Efficiency Decoration.

Australian Army Medical Corps.—Major R. H. Small.

ROYAL AUSTRALIAN AIR FORCE.

Citizen Air Force.

Medical Branch.

Frank Fairfax Ellis, M.B., B.S., is granted a commission on probation as Flight Lieutenant, 13th November, 1939; Ian Ross Horn, M.B., Ch.B., is granted a commission on probation as Flight Lieutenant, 20th November, 1939; Squadron Leader, E. T. Cato, M.C., relinquishes his commission on being appointed to a commission in the Royal Air Force Volunteer Reserve, 24th October, 1939; Flight Lieutenant S. J. M. Goulston relinquishes his commission, 2nd November, 1939.

Nominations and Elections.

THE undermentioned has applied for election as a member of the New South Wales Branch of the British Medical Association:

Pockley, Francis John Antill, M.B., B.S., 1936 (Univ. Sydney), 233, Macquarie Street, Sydney.

Books Received.

SYMPOSIUM ON THE SYNAPSE, by H. S. Grasser, J. Erlanger, D. W. Bronk, R. L. De Nó and A. Forbes, reprinted from The Journal of Neurophysiology; 1939. Springfield: C. C. Thomas. Imperial 8vo, pp. 111, with illustrations.

DIE BIOLOGISCHE REAKTION. EINE FUNKTIONELLE ANALYSE UND SYNTHESE BIOMETRISCHER WERTE ZUR ZAHLENMASSIGEN ERFASSUNG VON ALLERGIE, ALLGEMEINER RESISTENZ, SPEZIFISCHER RESISTENZ, KRANKHEITSINTENSITÄT EXTENSITÄT AKTIVER HERDE IMMUNITÄT, by O. H. Bucher-Trümpler and C. C. Hoffin-Karwatski; 1939. Bern: Hans Huber. Imperial 8vo, pp. 262, with illustrations. Price: Schw. Fr. 42.80.

DIVERTICULA AND DIVERTICULITIS OF THE INTESTINE: THEIR PATHOLOGY, DIAGNOSIS AND TREATMENT, by H. C. Edwards, M.S., F.R.C.S., with a foreword by G. Gordon-Taylor, O.B.E., M.S., F.R.C.S.; 1939. Bristol: John Wright and Sons Limited. Medium 8vo, pp. 347, with illustrations. Price: 25s. net.

Diary for the Month.

DEC. 5.—New South Wales Branch, B.M.A.: Executive and Finance Committee, Organization and Science Committee.
DEC. 6.—Victorian Branch, B.M.A.: Annual meeting.
DEC. 6.—Western Australian Branch, B.M.A.: Council.
DEC. 7.—South Australian Branch, B.M.A.: Council.
DEC. 8.—Queensland Branch, B.M.A.: Annual Meeting.
DEC. 12.—New South Wales Branch, B.M.A.: Ethics Committee.
DEC. 12.—Tasmanian Branch, B.M.A.: Branch.
DEC. 14.—New South Wales Branch, B.M.A.: Branch.
DEC. 15.—Queensland Branch, B.M.A.: Council.
DEC. 19.—New South Wales Branch, B.M.A.: Medical Politics Committee.
DEC. 29.—Tasmanian Branch, B.M.A.: Council.

Medical Appointments Vacant, etc.

For announcements of medical appointments vacant, assistants, *locum tenentes* sought, etc., see "Advertiser", pages xv ii-xx.

BALLARAT AND DISTRICT BASE HOSPITAL, BALLARAT, VICTORIA: Resident Medical Officers.
CHILDREN'S HOSPITAL (INC.), PERTH, WESTERN AUSTRALIA: Junior Resident Medical Officers.
DEPARTMENT OF PUBLIC HEALTH, PERTH, WESTERN AUSTRALIA: Resident Medical Officer.
KOORDA ROAD BOARD, KOORDA, WESTERN AUSTRALIA: Medical Officer.
MATER MISERICORDIÆ PUBLIC HOSPITALS, BRISBANE, QUEENSLAND: Resident Medical Officers.
PUBLIC SERVICE COMMISSIONER, ADELAIDE, SOUTH AUSTRALIA: Temporary Medical Officer.
RENWICK HOSPITAL FOR INFANTS, SUMMER HILL, NEW SOUTH WALES: Resident Medical Officer.
ROYAL NORTH SHORE HOSPITAL OF SYDNEY, NEW SOUTH WALES: Junior Resident Medical Officers.
ROYAL HOBART HOSPITAL, HOBART, TASMANIA: Resident Medical Officer.
SYDNEY HOSPITAL, SYDNEY, NEW SOUTH WALES: Senior Resident Medical Officer.
ST. GEORGE DISTRICT HOSPITAL, KOGARAH, NEW SOUTH WALES: Relieving Honorary Assistant Obstetrician.
THE PRINCE HENRY HOSPITAL, LITTLE BAY, SYDNEY, NEW SOUTH WALES: Prince Henry Hospital Medical and Surgical Fellowships.
VICTORIAN EYE AND EAR HOSPITAL, MELBOURNE, VICTORIA: Resident Surgeons.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment referred to in the following table without having first communicated with the Honorary Secretary of the Branch named in the first column, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

BRANCHES.	APPOINTMENTS.
NEW SOUTH WALES: Honorary Secretary, 135, Macquarie Street, Sydney.	Australian Natives' Association. Ashfield and District United Friendly Societies' Dispensary. Balmain United Friendly Societies' Dispensary. Leichhardt and Petersham United Friendly Societies' Dispensary. Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney. North Sydney Friendly Societies' Dispensary Limited. People's Prudential Assurance Company Limited. Phœnix Mutual Provident Society.
VICTORIAN: Honorary Secretary, Medical Society Hall, East Melbourne.	Associated Medical Services Limited. All Institutes or Medical Dispensaries. Australian Prudential Association, Proprietary, Limited. Federated Mutual Medical Benefit Society. Mutual National Provident Club. National Provident Association. Hospital or other appointments outside Victoria.
QUEENSLAND: Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17.	Brisbane Associate Friendly Societies' Medical Institute. Proserpine District Hospital. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.
SOUTH AUSTRALIAN: Secretary, 178, North Terrace, Adelaide.	All Lodge appointments in South Australia. All Contract Practice Appointments in South Australia.
WESTERN AUSTRALIAN: Honorary Secretary, 205, Saint George's Terrace, Perth.	Wiluna Hospital. All Contract Practice Appointments in Western Australia.

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